Protocol I3Y-MC-JPBM(a)

A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Nonsteroidal Aromatase Inhibitors (Anastrozole or Letrozole) plus LY2835219, a CDK4/6 Inhibitor, or Placebo in Postmenopausal Women with Hormone Receptor-Positive, HER2-Negative Locoregionally Recurrent or Metastatic Breast Cancer with No Prior Systemic Therapy in this Disease Setting

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Approval Date: 13-Nov-2015

1. Protocol 13Y-MC-JPBM(a)

A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Nonsteroidal Aromatase Inhibitors (Anastrozole or Letrozole) plus LY2835219, a CDK4/6 Inhibitor, or Placebo in Postmenopausal Women with Hormone Receptor-Positive, HER2-Negative Locoregionally Recurrent or Metastatic Breast Cancer with No Prior Systemic Therapy in this Disease Setting

Confidential Information

LY2835219

This study is a global, multicenter, double-blind, placebo-controlled, Phase 3 trial for postmenopausal women with hormone receptor-positive, HER2-negative locoregionally recurrent or metastatic breast cancer randomized to receive nonsteroidal aromatase inhibitors (anastrozole or letrozole) with or without LY2835219.

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Protocol Approved by Lilly: 03 September 2014
Amendment (a) Electronically Signed and Approved by Lilly on date provided below.

Approval Date: 13-Nov-2015 GMT

2. Synopsis

Study Rationale

LY2835219 is an oral, selective, and potent small molecule cyclin-dependent kinase (CDK) 4 and 6 (CDK4 and CDK6) dual inhibitor with antitumor activity within multiple preclinical pharmacology models and an acceptable toxicity profile in nonclinical species. LY2835219 mesylate has been shown to significantly inhibit tumor growth in multiple murine xenograft models for human cancer. Studies with LY2835219 across breast cancer cell lines indicate differential sensitivity to CDK4 and CDK6 inhibition based on histological and genetic characteristics. Growth inhibition in vitro across a diverse panel of 46 breast cancer cell lines, representing the known molecular subgroups of breast cancer, indicates that sensitivity to CDK4 and CDK6 inhibition is greater in estrogen receptor-positive (ER+) breast cancers with luminal histology.

LY2835219 has demonstrated evidence of single-agent clinical activity in a tumor-specific cohort of women with metastatic breast cancer (mBC). In Study I3Y-MC-JPBA (JPBA), 47 patients with a median of 7 prior systemic regimens received therapy with LY2835219. Among the 36 patients with hormone receptor-positive (HR+) mBC, there were 9 patients with confirmed partial responses (PR) for an objective response rate (ORR) of 25%. Further, of these 36 patients with HR+ mBC, the clinical benefiit rate (CBR: PR + stable disease [SD] 2'24 weeks) was 61%, and the disease control rate (DCR: PR + SD) was 80.6%. A total of 14 patients were continuing treatment at the time of analysis (Patnaik et al. 2014). In the same study, LY2835219 demonstrated an acceptable safety profile for women with HR+ mBC. The most common treatment-emergent adverse events (TEAEs) were diarrhea, nausea, fatigue, neutropenia, and vomiting. There were no treatment discontinuations attributable to an AE. The clinical activity and safety profile support further evaluation of LY2835219 in mBC.

Non-steroidal aromatase inhibitors (NSAI, letrozole and anastrazole) are approved and commonly used endocrine therapy in the first-line setting for postmenopausal women with HR+ mBC. The evaluation of LY2835219 in combination with an NSAI is of interest since both classes of drugs have acceptable and distinct safety profiles. The current study will assess if additional clinical benefit may be achieved in this disease setting with this drug combination.

Study I3Y-MC-JPBM (JPBM) is a randomized, double-blind, placebo-controlled, Phase 3 study evaluating treatment of LY2835219 with NSAI or placebo with NSAI in postmenopausal women with HR+, human epidermal growth factor receptor 2-negative (HER2-) locoregionally recurrent or metastatic breast cancer who have not received prior systemic therapy in this disease setting.

Clinical Protocol Synopsis: Study 13Y-MC-JPBM

Name of Investigational Product: LY2835219	
Title of Study: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Nonsteroidal Aromatase Inhibitors (Anastrozole or Letrozole) plus LY2835219, a CDK4/6 Inhibitor, or Placebo in Postmenopausal Women with Hormone Receptor-Positive, HER2-Negative Locoregionally Recurrent or Metastatic Breast Cancer with No Prior Systemic Therapy in this Disease Setting	
Number of Planned Patients: 450 Entered: 500 Enrolled/Randomized: 450 Completed: 450	**Phase of Development:** 3
Length of Study: approximately 91 months Planned first patient visit: Oct 2014 Planned last patient visit: May 2022 Planned interim analyses: 189 (approximately 70% of the planned) progression-free survival (PFS) events and 230 (approximately 85% of the planned) PFS events	
Objectives: The primary objective of Study I3Y-MC-JPBM is to compare treatment with LY2835219 plus NSAI therapy versus placebo plus NSAI therapy with respect to PFS in postmenopausal women with HR+, HER2- locoregionally recurrent or metastatic breast cancer who have not received prior systemic therapy in this disease setting. The secondary objectives of the study are to compare the combination treatment of LY2835219 and NSAI therapy versus placebo plus NSAI therapy with respect to the following: • overall survival [OS]; • OS rate at 1, 2, and 3 years; • ORR (complete response [CR] + PR); • duration of response [DoR] (CR + PR); • DCR (CR + PR + SD); • CBR (CR + PR + SD 2' 6 months); • safety and tolerability • change in symptom burden using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), EORTC QLQ-BR23 (breast) questionnaire, and health status scores from the EuroQol 5-Dimension 5 Level (EQ-5D 5L). • pharmacokinetics (PK) of LY2835219, its metabolites, and NSAI therapy The exploratory objectives are: • To explore potential biomarkers related to the mechanism of action of LY2835219, the cell cycle, and/or the pathogenesis of breast cancer. • To explore change in tumor size.	

Study Design: Study JPBM is a multicenter, randomized, double-blind, placebo-controlled Phase 3 study evaluating treatment of LY2835219 with NSAI or placebo with NSAI in postmenopausal women with HR+, HER2- locoregionally recurrent (not amenable to curative therapy) or metastatic breast cancer who have not received prior systemic therapy in this disease setting. Approximately 450 patients will be randomized 2:1 between the 2 arms. Patients will be randomized using the following stratification factors: nature of disease (visceral metastases versus bone-only metastases versus other) and prior (neo)adjuvant endocrine therapy (aromatase inhibitor therapy versus other versus no prior endocrine therapy).

Diagnosis and Main Criteria for Inclusion and Exclusions: Patients are eligible to be included in the study if they meet following criteria: 1) have a diagnosis of HR+, HER2- breast cancer; 2) have locoregionally recurrent disease not amenable to resection or radiation therapy with curative intent or metastatic disease; 3) have postmenopausal status due to either surgical/natural menopause or amenorrheic (non-treatment-induced) for at least 12 months; 4) have either measurable disease or nonmeasurable bone-only disease; 5) have a performance status :S1 on the Eastern Cooperative Oncology Group (ECOG) scale; 6) have adequate organ function; 7) have discontinued previous localized radiotherapy for palliative purposes or for lytic lesions at risk of fracture prior to randomization and recovered from the acute effects of therapy; 8) are female and 2'18 years of age; 9) are able to swallow capsules; 10) have given written informed consent prior to any study-specific procedures; 11) are reliable, willing to be available for the duration of the study, and are willing to follow study procedures.

Patients will be excluded from the study if they meet any of the following criteria: 12) have visceral crisis, lymphangitic spread, or leptomeningeal carcinomatosis; 13) have inflammatory breast cancer; 14) have clinical evidence or a history of central nervous system (CNS) metastasis; 15) are currently receiving or have previously received endocrine therapy for locoregionally recurrent or metastatic breast cancer; 16) have received prior (neo)adjuvant endocrine therapy with a disease-free interval :S12 months from completion of treatment; 17) are currently receiving or have previously received chemotherapy for locoregionally recurrent or metastatic breast cancer; 18) have received prior treatment with everolimus; 19) have received prior treatment with any CDK4 and CDK6 inhibitor (or participated in any CDK4 and CDK6 inhibitor clinical trial for which treatment assignment is still blinded); 20) have initiated bisphosphonates or approved RANK ligand (RANK-L) targeted agents <7 days prior to randomization; 21) are currently receiving an investigational drug in a clinical trial or participating in any other type of medical research judged not to be scientifically or medically compatible with this study; 22) have received treatment with a drug that has not received regulatory approval for any indication within 14 or 21 days of randomization for a nonmyelosuppressive or myelosuppressive agent, respectively; 23) have had major surgery within 14 days prior to randomization; 24) have received recent (within 28 days prior to randomization) yellow fever vaccination; 25) have serious preexisting medical conditions that, in the judgment of the investigator, would preclude participation in this study; 26) have a personal history of any of the following conditions: syncope of cardiovascular etiology, ventricular tachycardia, ventricular fibrillation, or sudden cardiac arrest; 27) have a history of any other cancer (except non-melanoma skin cancer or carcinoma in-situ of the cervix), unless in complete remission with no therapy for a minimum of 3 years; 28) have received an autologous or allogeneic stem-cell transplant; 29) have active bacterial or fungal infection or detectable viral infection.

Test Product, Dosage, and Mode of Administration: LY2835219 will be supplied as capsules administered orally, 150 mg every 12 hours on Days 1 to 28 of a 28-day cycle.

Planned Duration of Treatment:
Treatment period: until disease progression or other discontinuation criteria are fulfilled.
Short-term follow-up (postdiscontinuation): 30 days
Long-term follow-up (postdiscontinuation): until death

Reference Therapy, Dose, and Mode of Administration: Placebo will be supplied as capsules administered orally every 12 hours on Days 1 to 28 of a 28-day cycle. In both arms, either letrozole or anastrazole will be administered orally. Where required, anastrazole 1-mg or letrozole 2.5-mg tablets will be supplied.

Criteria for Evaluation:

Efficacy:

- PFS (Response Evaluation Criteria in Solid Tumors [RECIST] v1.1)
- OS
- OS at 1, 2, and 3 years
- ORR (RECIST v1.1)
- DoR (RECIST v1.1)
- DCR (RECIST v1.1)

Safety:

- AEs using MedDRA

Health Outcomes:

- EORTC QLQ-C30 and EORTC QLQ-BR23: Describe target tumor symptom changes
- EQ-5D 5L: Describe health status changes

Pharmacokinetics:

- Population PK parameters for LY2835219 and possibly LY2835219 metabolites and letrozole or anastraszole

Exploratory:

- Potential biomarkers related to the mechanism of action of LY2835219, the cell cycle, and/or the pathogenesis of breast cancer
- Time course of change in tumor size

Statistical Methods:

Statistical:
The primary objective of this study is to compare treatment with LY2835219 plus NSAI therapy versus placebo plus NSAI therapy with respect to progression-free survival (PFS) in postmenopausal women with HR+, HER2- locoregionally recurrent or metastatic breast cancer. An important secondary objective of this study is to compare the 2 arms with respect to OS.
A 3-look group sequential design on the primary endpoint of PFS will be utilized, with 2 interim analyses and 1 final PFS analysis occurring at approximately 189, 230, and 270 investigator-assessed PFS events,, respectively. A fixed alpha-spending method will be used to maintain the cumulative 1-sided type I error rate of .025. Assuming a hazard ratio of 0.67, this design yields more than 80% statistical power to detect superiority of the LY2835219 plus NSAI arm over placebo plus NSAI arm with the use of a 1-sided log-rank test and a cumulative type I error rate of 0.025.
OS is an important secondary endpoint for this study. OS will be tested only if the test of PFS is significant. The final OS analysis will occur after approximately 315 OS events have been observed.

Efficacy:
The PFS and OS analyses to test the superiority of LY2835219 to placebo in improving PFS and OS will use the log-rank test stratified by the stratification variables. Additional analyses will be performed using the Kaplan-Meier method to estimate the PFS and OS curves and rates, and the Cox proportional hazard model will be used to estimate the PFS and OS hazard ratios and corresponding 95% confidence interval.

Safety:
All safety summaries and analyses will be based on the Safety Population, defined as all enrolled patients receiving at least 1 dose of study treatment. Patients will be grouped according to treatment received in Cycle 1.

Health Outcomes:
Change in pain and symptom burden willll be analyzed descriptively and treatment arms will be compared using a repeated measures model, where appropriate.

Pharmacokinetics:
PK parameters for LY2835219 in plasma (clearanc , exposure, volume of distribution, and half-lives) and inter-individual PK variability will be computed using nonlinear mixed effect modeling implemented in NONMEM. If warranted by the data, PK parameters for LY2835219 metabolites and anastrozole or letrozole in plasma and inter-individual variability estimates will also be computed using nonlinear mixed-effect modeling implemented in NONMEM.

Pharmacodynamics:
Pharmacodynamic data (such as neutrophil, lymphocytes, or platelets counts in blood) may be analyzed by means of NONMEM and connected to the population PK model for LY2835219 and/or anastrozole or letrozole in a PK/pharmacodynamic model.

Biomarkers:
Summary statistics will include means, medians, corresponding standard errors, quartiles, and ranges. Biomarkers with discrete measures, such as genotype locus, will be summarized in frequency tables. Correlative analyses may be performed to investigate associations between biomarkers and clinical endpoints.

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4. Abbreviations and Definitions

Term	Definition
AE	Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
audit	A systematic and independent examination of the trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, applicable standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).
blinding/masking	A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Unless otherwise specified, blinding will remain in effect until final database lock. A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the patient is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the patient are not. A double-blind study is one in which neither the patient nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the patients are aware of the treatment received.
CAP	College of American Pathologists
CBR	clinical benefit rate
CDK	cyclin-dependent kinase
CI	confidence interval
CNS	central nervous system

collection database	A computer database where clinical trial data are entered and validated.
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
continued access period	The period between study completion and end of trial during which patients on study therapy who continue to experience clinical benefit may continue to receive study therapy until one of the criteria for discontinuation is met.
CR	complete response
CRF/eCRF	case report form/electronic case report form Sometimes referred to as clinical report form: A printed or electronic form for recording study participants' data during a clinical study, as required by the protocol.
CRP	clinical research physician Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTS	change in tumor size A measure of tumor dynamics from which tumor response is derived. Tumor size is the sum of tumor measurements across all target tumors at a given evaluation (RECIST criteria).
DCR	disease control rate
DMC	Data Monitoring Committee
DoR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group

end of trial	End of trial is the date of the last visit or last scheduled procedure for the last patient.
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.
enter	Patients entered into a trial are those who sign the informed consent form.
EORTC QLQ-BR23	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Breast Cancer
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EQ-5D 5L	EuroQol 5-Dimension 5 Level
ER+	estrogen receptor-positive
ERB/IRB	ethical review board/institutional review board A board or committee (institutional, regional, or national) composed of medical and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the patients participating in a clinical trial are protected.
GCP	good clinical practice
H_0	null hypothesis
H_a	alternative hypothesis
HER2-	human epidermal growth factor receptor 2-negative
HIV	human immunodeficiency virus
HR+	hormone receptor-positive
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IHC	immunohistochemistry

Informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical trial data, separated into treatment groups that is conducted before the final reporting database is created/locked.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial.
investigator	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principall investigator.
IRC	Internal Review Committee
ITT	intention-to-treat The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IWRS	interactive web-response system
legal representative	An individual, judicial, or other body authorized under applicable law to consent on behalf of a prospective patient to the patient's participation in the clinical study.
Lilly Safety System	Global safety database that tracks and reports serious adverse and spontaneous events occurring while using a drug/drug delivery system.
LLT	Lower Level Term
mBC	metastatic breast cancer
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NSAI	nonsteroidal aromatase inhibitor

ORR	objective response rate
OS	overall survival
patient	A study participant who has the disease or condition for which the investigational product is targeted.
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PgR	progesterone receptor
PK	pharmacokinetic
PR	partial response
PS	performance status
PT	Preferred Term
QTc	corrected QT interval
randomize	the processs of assigning patients to an experimental group on a random basis
RANK-L	receptor activator of nuclear factor kappa-B ligand
Rb	retinoblastoma
REC1ST	Response Evaluation Criteria in Solid Tumors
reporting database	A point-in-time copy of the collection database. The final reporting database is used to produce the analyses and output reports for interim or final analyses of data.
re-screen	to screen a patient who was previously declared a screen failure for the same study
SAE	serious adverse event
SAP	Statistical Analysis Plan

screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study. In this study, screening involves invasive or diagnostic procedures and/or tests (for example, diagnostic psychological tests, X-rays, blood draws). For this type of screening, informed consent for these screening procedures and/or tests shall be obtained; this consent may be separate from obtaining consent for the study.
screen failure	patient who does not meet one or more criteria required for participation in a trial
SD	stable disease
SMD	Senior Management Designee
SOC	System Organ Class
study completion	This study will be considered complete after the final analysis/evaluation of overall survival is performed.
SUSARs	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event Any untoward medical occurrence that either occurs or worsens at any time after treatment baseline and that does not necessarily have to have a causal relationship with this treatment.
ULN	upper limit of normal
VAS	visual analog scale

A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Nonsteroidal Aromatase 1nhibitors (Anastrozole or Letrozole) plus LY2835219, a CDK4/6 1nhibitor, or Placebo in Postmenopausal Women with Hormone Receptor-Positive, HER2-Negative Locoregionally Recurrent or Metastatic Breast Cancer with No Prior Systemic Therapy in this Disease Setting

5. 1ntroduction

Breast cancer is one of the most common cancers in women. In 2012, there were approximately 1.7 million new cases of breast cancer worldwide; since 2008, the worldwide incidence of breast cancer has increased by more than 20% and mortality has increased by 14% (Bray et al. 2013; Ferlay et al. 2013). While early stage disease is treatable, patients with metastatic breast cancer (mBC) have a median overall survival (OS) of only 2 to 3 years (Cardoso et al. 2012). The treatment for women diagnosed with hormone receptor positive (HR+) mBC includes endocrine therapy. In postmenopausal women, aromatase inhibitors (including anastrozole and letrozole) are recommended for the initial treatment of mBC, if not used in the adjuvant setting or if discontinued for at least 12 months (Cardoso et al. 2012). However, de novo or acquired resistance to adjuvant endocrine therapy and metastatic breast cancer remains an important clinical challenge.

Cyclin D1 interacts with cyclin-dependent kinases 4 and 6 (hereafter CDK4 and CDK6) in an active protein complex that promotes cell proliferation (Velasco-Velazquez et al. 2011). Many HR+ breast cancers demonstrate an intact retinoblastoma tumor suppressive function, however, overexpression of cyclin D1 protein by oncogenic signaling occurs in approximately 30% to 50% of cancers. Cyclin D1 is regarded as the most frequently overexpressed gene in primary breast cancer, with amplification of the encoding gene, CCND1, occurring in approximately 15% of breast cancers (Casimiro et al. 2014). Therefore, CDK4 and CDK6 represents a potential therapeutic target for HR+ breast cancer. Consequently, further evaluation of CDK4 and CDK6 inhibitorss to improve clinical outcomes for women with HR+ breast cancer is warranted.

During the cell cycle, the G1 restriction point controls entry into S phase and is essential for proper regulation of cell proliferation (Sherr 1996; Ortega et al. 2002). CDK4 and CDK6 participates in a complex with the D-type cyclins to initiate progression through the G1 restriction point. The CDK4 and CDK6 - cyclin D1 complex regulates the G1 restriction point through phosphorylation and inactivation of the retinoblastoma (Rb) tumor suppressor protein, thereby promoting S phase entry. Alterations in this pathway occur frequently in human cancers and involve: 1) loss of functional CDK inhibitors through deletion or epigenetic silencing; 2) activating mutations and/or overexpression of CDK4 and CDK6 or the D-type cyclins; and 3) loss of functional Rb through mutation or deletion. Except for tumors with functional loss of Rb, which functions downstream of the CDK4 and CDK6 - cyclin D1 complex, most cancers are potentially sensitive to pharmacologic inhibition of CDK4 and

CDK6. From a therapeutic standpoint, the goal of inhibiting CDK4 and CDK6 with a small molecule is to prevent cell cycle progression through the G1 restriction point, thus arresting tumor growth.

LY2835219 represents a selective and potent small molecule inhibitor of CDK4 and CDK6 with acceptable physical characteristics, pharmacokinetic (PK) properties, and safety profile in nonclinical species. There may be important opportunities to tailor therapy with LY2835219 for patients with breast cancer. Specifically, studies with LY2835219 indicate differential sensitivity to CDK4 and CDK6 inhibition based on histological and genetic characteristics. Growth inhibition in vitro across a diverse panel of 46 breast cancer cell lines, representing the known molecular subgroups of breast cancer, indicates that sensitivity to CDK4 and CDK6 inhibition is greater in ER+ breast cancers with luminal histology. In accordance with the known biology of CDK4 and CDK6, the results also indicate that many of these sensitive cell lines are also characterized as having amplification of CCND1, which is the gene that encodes cyclin D1. These results are consistent with previous studies which demonstrate that effective induction of G1 cell cycle arrest by LY2835219 is dependent upon the presence of Rb.

Findings from the Phase 1 Study JPBA indicate that the LY2835219 single-agent maximum tolerated dose of 200 mg administered orally every 12 hours demonstrates an acceptable safety profile. LY2835219 has demonstrated evidence of clinical activity in women with mBC at doses of both 150 mg and 200 mg every 12 hours. Additionally, preliminary analysis of PK data from Study JPBA for LY2835219 as a single agent at 150 mg and 200 mg every 12 hours indicates that the range of steady-state exposures is comparable for the 2 doses. In Study JPBA, 47 patients with a median of 7 prior systemic regimens received therapy with LY2835219. In the mBC cohort, the most common treatment-emergent adverse events (TEAEs) possibly related to study drug included diarrhea, nausea, fatigue, neutropenia, and vomiting. Among 36 patients with HR+ mBC receiving LY2835219, there were 9 patients with confirmed partial responses (PR) for an objective response rate of 25%. Further, in these 36 patients, the clinical benefit rate (CBR; PR + stablle disease [SD] ≥24 weeks) was 61%, and the disease control rate (DCR; [PR + SD]) was 80.6%. A total of 14 patients were continuing treatment at the time of analysis (Patnaik et al. 2014).

Study JPBA findings support further investigation of LY2835219 in combination with standard endocrine therapy for women with HR+ locoregionally recurrent or metastatic breast cancer. Non-steroidal aromatase inhibitors (NSAI, anastrazole and letrozole) are approved and commonly used endocrine therapy in the first-line setting for postmenopausal women with HR+ mBC. The evaluation of LY2835219 in combination with an NSAI is of interest since both classes of drugs have acceptable and distinct safety profiles. Safety and tolerability of LY2835219 in combination with endocrine therapies (including anastrozole and letrozole) are being further evaluated in patients with HR+, HER2- mBC, in an ongoing Phase 1b study, I3Y-MC-JPBH (JPBH). As of 21 July 2014, 35 patients received at least one dose of combination therapy (20 with letrozole, 15 with anastrazole). Preliminary safety data from Study JPBH have shown a consistent adverse event profile for LY2835219 administered at 200 mg every 12 hours

in combination with NSAI as was observed in the Study JPBA mBC single-agent cohort. However, at the 200 mg dose, the incidence of treatment-emergent Grade 3 diarrhea was greater in combination with NSAI than when LY2835219 was administered alone (25.7% and 13.6%, respectively). Clinical and PK findings from the single-agent Phase 1 Study JPBA and preliminary safety data from the LY2835219/NSAI combination in Study JPBH support 150 mg every 12 hours as the recommended dose for LY2835219 in Study I3Y-MC-JPBM (JPBM).

The current Phase 3 Study JPBM will evaluate the clinical safety and efficacy of NSAI plus LY2835219 or placebo in postmenopausal women with HR+, HER2- locoregionally recurrent (not amenable to curative therapy) or metastatic breast cancer who have not previously received systemic therapy in this disease setting.

More information about the known and expected benefits and risks of LY2835219 may be found in the Investigator's Brochure (IB). Information on AEs expected to be related to the LY2835219 may be found in Section 7 (Development Core Safety Information) of the IB. Information on serious adverse events (SAEs) expected in the study population independent of drug exposure and that will be assessed by the sponsor in aggregate, periodically during the course of the study, may be found in Section 6 (Effectss in Humans) of the IB.

More detailed information about the known and expected benefits and risks of anastrozole or letrozole may be found in the following: Patient Information Leaflet, Package Insert, or Summary of Product Characteristics.

5.1. Rationale for Amendment (a)

Study JPBM protocol was amended to update the dosing guidance for cases of hematologic toxicity and diarrhea and guidance on the use of blood cell growth factors. Lilly conducted a review across several clinical trials of abemaciclib in breast cancer and concluded that there were some inconsistencies. This amendment will harmonize the dosing guidance and clarify that blood cell growth factors are only to be used in a manner consistent with American Society of Clinical Oncology (ASCO) guidelines.

Further modifications were performed for clarity with supportive management for diarrhea and coadministration with substrate drugs of CYPs with narrow therapeutic margin.

Furthermore, the statistical analysis plan (SAP) was updated. The number of events required to perform the final PFS analysis was decreased from 312 events to 270 events based on the following rationale. The results of PALOMA-1 (palbociclib + letrozole vs letrozole) and PALOMA-3 (palbociclib + fulvestrant vs fulvestrant) indicate the effect of CDK 4 and 6 inhibitors in combination with endocrine therapy may have a larger effect than was originally assumed during the development of this protocol. As a result, the assumed hazard ratio has been changed from 0.714 (corresponding to an increase in median PFS from 10 months to 14 months) to 0.67 (increase in median PFS from 10 months to 15 months). In addition, the interim analysis boundaries, timing of interim analyses, and OS analysis plan were modified.

Minor typographical and formatting edits were made throughout the document for clarity and consistency.

6. Objectives

6.1. Primary Objective

The primary objective of this study is to compare treatment with LY2835219 plus NSAI therapy versus placebo plus NSAI therapy with respect to PFS in postmenopausal women with HR+, HER2- locoregionally recurrent or metastatic breast cancer who have not received prior systemic therapy in this disease setting.

6.2. Secondary Objectives

The secondary objectives of the study are to compare the combination treatment of LY2835219 and NSAI therapy versus placebo plus NSAI therapy with respect to the following:

- OS;
- OS rate at 1, 2, and 3 years;
- ORR (CR + PR);
- duration of response (CR + PR);
- DCR (CR + PR + SD);
- CBR (CR + PR + SD 2'6 months);
- the safety and tolerability;
- change in symptom burden from baseline using the EORTC QLQ-C30, EORTC QLQ-BR23 (breast) questionnaire, and health status scores from the EQ-5D 5L; and
- the PK of LY2835219, its metabolites, and NSAI therapy.

6.3. Exploratory Objectives

- To explore potential biomark rs related to the mechanism of action of LY2835219, the cell cycle, and/or the pathogenesis of breast cancer.
- To explore change in tumor size.

7. Study Population

Individuals who do not initially meet the criteria for participation in this study (screen failure) may be re-screened (Section 7.2.1).

Study participants should be instructed not to donate blood or blood products during the study or for 2 weeks following the last dose of study drug.

Prospective approval of protocol deviations to recruitment and enrollment criteria (also known as protocol waivers or exemptions) is not permitted.

7.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet **all** off the following criteria:

1. have a diagnosis of HR+, HER2- breast cancer. Although not required as a protocol procedure, metastatic disease should be considered for biopsy whenever possible to reassess HR and HER2 status if clinically indicated.
    - To fulfill the requirement for HR+ disease, a breast cancer must express, by immunohistochemistry (IHC), at least one of the hormone receptors (ER, progesterone receptor [PgR]) as defined in the relevant American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) Guidelines (Hammond et al. 2010).
    - To fulfill the requirement of HER2- disease, a breast cancer must not demonstrate, at initial diagnosis or upon subsequent biopsy, overexpression of HER2 by either IHC or in-situ hybridization (ISH) as defined in the relevant ASCO/CAP guidelines (Wolff et al. 2013).
2. have locoregionally recurrent disease not amenable to resection or radiation therapy with curative intent or metastatic disease
3. have postmenopausal status, defined as meeting one of the following conditions:
    - Prior bilateral ophorectomy
    - Age ≥60 years
    - Age <60 years and amenorrheic (non-treatment-induced amenorrhea secondary to tamoxifen, toremifene, ovarian suppression, or chemotherapy) for at least 12 months. Follicle-stimulating hormone (FSH) and estradiol must be in the postmenopausal range.

[4] have one of the following as defined by the RECIST v1.1 (Eisenhauer et al. 2009; refer to Attachment 5):

- Measurable disease
- Nonmeasurable bone-only disease. Nonmeasurable bone-only disease may include any of the following: blastic bone lesions, lytic bone lesions without a measurable soft tissue component, or mixed lytic-blastic bone lesions without a measurable soft tissue component.

[5] have a PS of ≤1 on the ECOG scale (see Attachment 4)

[6] have adequate organ function, including:

- hematologic: absolute neutrophil count (ANC) ≥1.5 x 10^9/L, platelets ≥100 x 10^9/L, and hemoglobin ≥8 g/dL. Patients may receive erythrocyte transfusions to achieve this hemoglobin level at the discretion of the investigator; however, initial study drug treatment must not begin earlier than the day after the erythrocyte transfusion.
- hepatic: bilirubin ≤1.5 times the upper limit of normal (ULN) and alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3.0 times ULN (or ALT and AST ≤5 times ULN if liver metastases are present).
- renal: serum creatinine ≤1.5 times ULN.

[7] have discontinued previous localized radiotherapy for palliative purposes or for lytic lesions at risk of fracture at least 2 weeks prior to randomization and recovered from the acute effects of therapy (until the toxicity resolves to either baseline or at least Grade 1) except for residual alopecia or peripheral neuropathy.

[8] are female and ≥18 years of age

[9] are able to swallow capsules

[10] have given written informed consent prior to any study-specific procedures

[11] are reliable, willing to be available for the duration of the study, and are willing to follow study procedures.

7.2. Exclusion Criteria

Patients will be excluded from the study if they meet **any** of the following criteria:

[12] have visceral crisis, lymphangitic spread, or leptomeningeal carcinomatosis. Visceral crisis is not the mere presence of visceral metastases but implies severe organ dysfunction as assessed by symptoms and signs, laboratory studies, and rapid progression of the disease.

[13] have inflammatory breast cancer.

[14] have clinical evidence or a history of CNS metastasis. Screening is not required for enrollment.

[15] are currently receiving or have previously received endocrine therapy for locoregionally recurrent or metastatic breast cancer. [Note: A patient may be enrolled if she received prior (neo)adjuvant endocrine therapy (including , but not limited to anti-estrogens or aromatase inhibitors) for localized disease. In addition, a patient may be enrolled if she has received :S2 weeks of NSAI in this disease setting immediately preceding screening and agrees to discontinue NSAI until study treatment initiation.]

[16] have received prior (neo)adjuvant endocrine therapy (e.g., anti-estrogens or aromatase inhibitors) with a disease-free interval :S12 months from completion of treatment.

[17] are currently receiving or have previously received chemotherapy for locoregionally recurrent or metastatic breast cancer. [Note: Patients may be enrolled if they received prior (neo)adjuvant chemotherapy for localized disease.]

[18] have received prior treatment with everolimus

[19] have received prior treatment with any CDK4 and CDK6 inhibitor (or participated in any CDK4 and CDK6 inhibitor clinical trial for which treatment assignment is still blinded)

[20] have initiated bisphosphonates or approved RANK ligand (RANK-L) targeted agents (for example, denosumab) <7 days prior to randomization

[21] are currently receiving an investigational drug in a clinical trial or participating in any other type of medical research judged not to be scientifically or medically compatible with this study. If a patient is currently enrolled in a clinical trial involving non-approved use of a device, then agreement with the investigator and Lilly clinical research physician (CRP) is required to establish eligibility.

[22] have received treatment with a drug that has not received regulatory approval for any indication within 14 or 21 days of randomization for a nonmyelosuppressive or myelosuppressive agent, respectively.

[23] have had major surgery within 14 days prior to randomization to allow for post-operative healing of the surgical wound and site(s).

[24] have received recent (within 28 days prior to randomization) yellow fever vaccination.

[25] have serious preexisting medical conditions that, in the judgment of the investigator, would preclude participation in this study (for example, history of major surgical resection involving the stomach or small bowel, or preexisting Crohn's disease or ulcerative colitis).

[26] have a personal history within the last 12 months of any of the following conditions: syncope of cardiovascular etiology, ventricular tachycardia, ventricular fibrillation, or sudden cardiac arrest.

[27] have a history of any other cancer (except non-melanoma skin cancer or carcinoma in-situ of the cervix), unless in complete remission with no therapy for a minimum of 3 years.

[28] have received an autologous or allogeneic stem-cell transplant.

[29] have active bacterial or fungal infection or detectable viral infection (for example, human immunodeficiency virus [HIV] or viral hepatitis). Screening is not required for enrollment.

7.2.1. Rescreening

A patient who fails screening is allowed to screen again after signing a new informed consent form (ICF) and will be assigned a new patient number under the conditions specified in this section.

The following patients may be eligible for rescreening if any of the following circumstances:

- Patients who have become eligible to enroll in the study as the result of a protocol amendment.
- Patient status has changed such that the eligibility criterion that caused the patient to screen fail would no longer cause the patient to screen fail again.
- Patients who complete screening and meet all inclusion and exclusion requirements but are unable to be enrolled due to extenuating circumstances (such as, severe weather, death in family, child illness).

The investigator should contact the Lilly CRP prior to rescreening a patient.

7.3. Discontinuations

7.3.1. Discontinuation of Patients

The criteria for enrollment must be followed explicitly. If the investigator site identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, the sponsor must be notified. If the sponsor identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, the investigator site will be notified. A discussion must occur between the sponsor CRP and the investigator to determine whether the patient may continue in the study, with or without study drug. Inadvertently enrolled patients may be maintained in the study and on study drug when the Lilly CRP agrees with the investigator that it is medically appropriate for that patient. The patient may not continue in the study with or without study drug if the Lilly CRP does not agree with the investigator's determination it is medically appropriate for the patient to continue. The investigator must obtain documented approval from the Lilly CRP to allow the inadvertently enrolled patient to continue in the study with or without study drug.

In addition, patients will be discontinued from the study treatment (that is, blinded study drug and/or NSAI) and/or from the study in the following circumstances:

- progressive disease (PD) as defined by RECIST v1.1

- enrollment in any other clinical trial involving an investigational drug or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- investigator decision
    - the investigator decides that the patient should be discontinued from the study or study treatment
    - if the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study treatment occurs prior to introduction of the new agent
- patient decision
    - the patient or the patient's designee (for example, legal guardian) reque ts to be withdrawn from the study or study treatment
- sponsor decision
    - Lilly stops the study or stops the patient'ss participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)

The reason and date of discontinuation will be collected for all patien s. All randomized patients who discontinue regardless of whether or not they received study d ug, will have procedures performed as shown in the Study Schedule (Attachment 1).

7.3.2. Discontinuation of Study Sites

Study site participation may be discontinued if Lilly, t e investigator, or the ethical review board (ERB) of the study site judges it necessary for medical, safety, regulatory, ethical, or other reasons consistent with applicable laws, regulations, and GCP.

7.3.3. Discontinuation of the Study

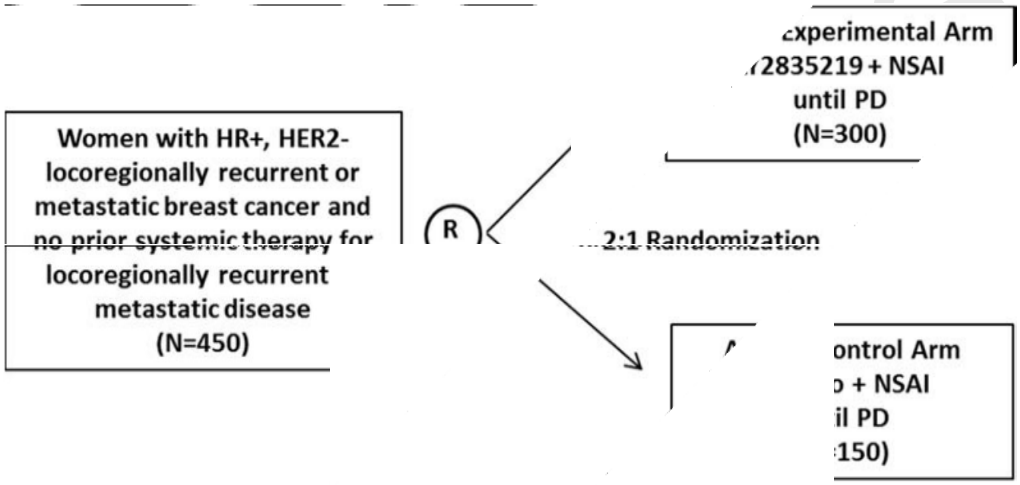
The study will be discontinued if Lilly judges it necessary for medical, safety, regulatory, ethical, or other reasons cor nt with applicable laws, regulations, and GCP.

8. 1nvestigational Plan

8.1. Summary of Study Design

Study JPBM is a multicenter, randomized, double-blind, placebo-controlled, Phase 3 study evaluating treatment of LY2835219 with NSAI or placebo with NSAI in postmenopausal women with HR+, HER2- locoregionally recurrent (not amenable to curative therapy) or metastatic breast cancer who have not received prior systemic therapy in this disease setting .

Figure JPBM.8.1 illustrates the study design.



Abbreviations: HER2- = human epidermal growth factor receptor 2-negative; HR+ = hormone receptor-positive; N = number; NSAI = nonsteroidal aromatase inhibitor; PD = progressive disease.

Figure JPBM.8.1. 1llustration of study design.

Approximately 450 patients will be randomized 2:1 between the 2 arms:

- Experimental Arm A: LY2835219 150 mg orally every 12 hours on Days 1 to 28 plus either anastrozole 1 mg or letrozole 2.5 mg once daily of a 28-day cycle
- Control (Placebo) Arm B: Placebo orally every 12 hours on Days 1 to 28 plus either anastrozole 1 mg or letrozole 2.5 mg once daily of a 28-day cycle

Patients will be randomized using the following stratification factors: nature of disease (visceral metastases versus bone-only metastases versus other) and prior (neo)adjuvant endocrine therapy (aromatase inhibitor therapy versus other versus no prior endocrine therapy). The presence of visceral metastases refers to lung, liver, pleural, peritoneal, or adrenal gland involvement at the time of randomization. Prior (neo)adjuvant endocrine therapy refers to aromatase inhibitor therapy (e.g., anastrozole, exemestane and letrozole) vs. other (e.g., tamoxifen and fulvestrant) vs. no prior endocrine therapy.

Database lock for the interim analyses for efficacy will occur when approximately 189 and 230 investigator-assessed PFS events have been observed. Database lock for the final analysis of the PFS endpoint will occur when approximately 270 investigator-assessed PFS events have

been observed. The final analysis of OS will occur when approximately 315 OS events have been observed. All patients will be followed for survival information until death or study completion, whichever comes first.

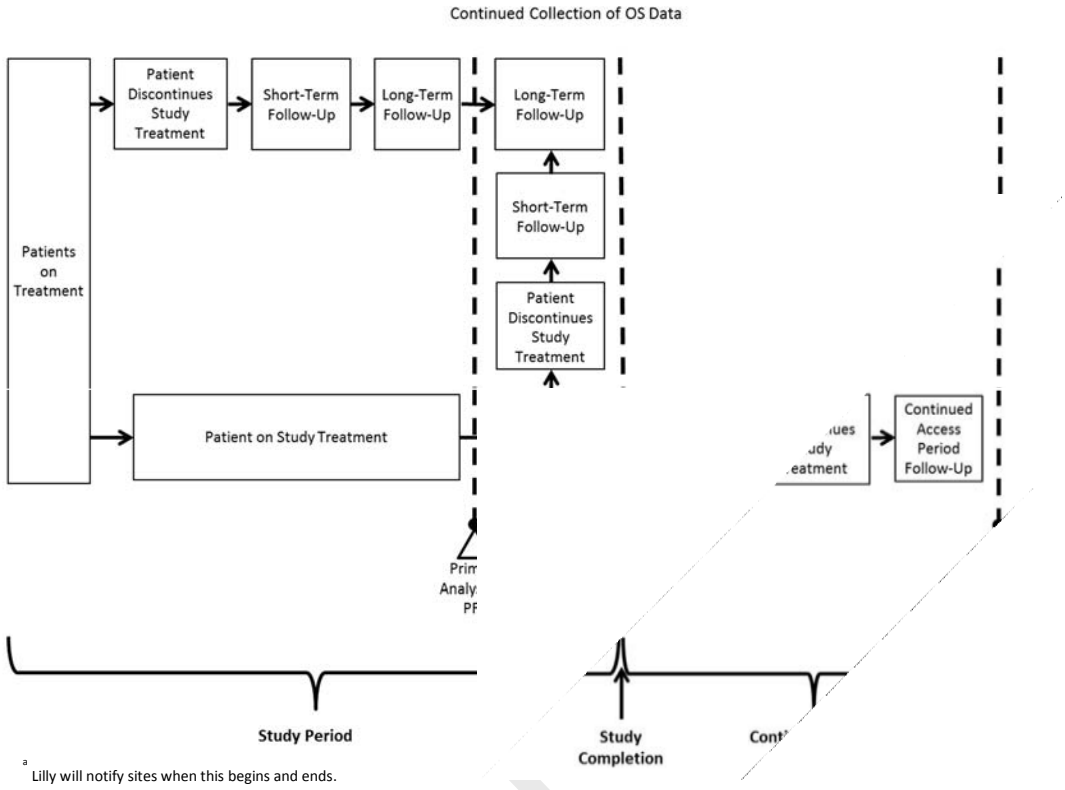
Terms used to describe the periods during the study are defined below:

- **Baseline:** begins when the ICF is signed and ends at the first study treatment dose (or at discontinuation, if no treatment is given). This may be up to 28 days prior to the first study treatment dose.
- **Study Period:** begins at the first study treatment dose and ends at study completion. The study period does not include the continued access period.
    - **Study Treatment Period:** begins at the first study treatment dose and ends when the patient and the investigator agree that the patient will no longer continue study treatment. This date is to be reported on the electronic case report form (eCRF) as the Date of Discontinuation from study treatmentt.
- **Postdiscontinuation Follow-Up:** begins the day after the patient and the investigator agree that the patient will no longer continue study treatment.
    - ***Short-term follow-up*** begins the day after the patient and the investigator agree that the patient will no longer continue study treatment and lasts approximately 30 days.
    - ***Long-term follow-up*** begins the day after short-term follow-up is completed and continues until the patient's death or overall study completion.
- **Continued Access Period:** begins after study completion and ends at the end of trial. During the continued access period, patients on study treatment who continue to experience clinical benefit may continue to receive study treatment (except placebo) until one of the criteria for discontinuation is met.
    - The continued access period includes continued access period short-term follow-up.
    - Continued access short-term follow-up: begins the day after the patient and the investigator agree that the patient will no longer continue treatment in the continued access period and lasts approximately 30 days.

8.1.1. Study Completion and End of Trial

This study will be considered complete (that is, the scientific evaluation will be complete [study completion]) following the evaluation of final OS data (refer to Figure JPBM.8.2) as determined by Lilly. Investigators will continue to follow the study schedule for all patients until notified by Lilly that study completion has occurred.

"End of trial" refers to the date of the last visit or last scheduled procedure for the last patient. The end of trial occurs after study completion and after the last patient has discontinued study treatment and completed continued access period follow-up (Figure JPBM.8.2).



[a] Lilly will notify sites when this begins and ends.

Abbreviations: OS = overall survival; PFS = progression-free survival.

Figure JPBM.8.2. Study period and continued access period diagram.

8.1.2. Continued Access Period

After study completion, all patients who are on study treatment and who are eligible for the continued access period will be unblinded. Patients receiving study treatment and experiencing ongoing clinical benefit may continue to receive study treatment in the continued access period until one of the criteria for discontinuation is met (Section 7.3.1). During the continued access period, placebo will no longer be administered, and crossover will not be permitted. Lilly will notify investigators when the continued access period begins.

Patients who are in short-term follow-up when the continued access period begins will continue in short-term follow-up until the 30-day short-term follow-up visit is completed. Long-term follow-up does not apply.

Patients who are in long-term follow-up when the continued access period begins will be discontinued from long-term follow-up.

During the continued access period, all AEs, SAEs, and study drug exposure will be reported on the CRF. Serious adverse events will also be reported to Lilly Global Patient Safety (see Section 10.3.1). In the event that an SAE occurs, Lilly may request additional information (such as local laboratory results, concomitant medications, and hospitalizations) in order to evaluate the reported SAE.

Investigators will perform any other standard procedures and tests needed to treat and evaluate patients; however, the choice and timing of the tests will be at the investigator's discretion. Lilly will not routinely collect the results of these assessments.

8.2. Discussion of Design and Control

A randomized, controlled design is being used in this study. Randomization minimizes systematic bias in the selection and assignment of patients to study therapy and provides justification for inferential statistical methods to be used on data from this study. Using an appropriate concurrent control arm enables direct statistical estimation of benefits and harms due to study therapy and minimizes bias in the assessment and interpretation of observed treatment effects. Patients will be stratified for differences in factors thought to be associated with clinical outcomes to further reduce the potential for bias and improve the power of the analyses. Assessment of bias is further minimized by the use of a double blind and placebo control (see Section 9.3).

Investigational treatment administration in this study is double-blind; that is, patients, investigational sites, and the sponsor study team do not have immediate access to investigational treatment assignments for any patients. This design feature minimizes potential bias due to knowledge of patient's treatment during evaluation of study endpoints, at the patient level or aggregated across patients.

9. Treatment

9.1. Treatments Administered

The following treatments will be administered in this study:

- Experimental Arm A: LY2835219 150 mg orally every 12 hours plus either anastrozole 1 mg or letrozole 2.5 mg orally every 24 hours on Days 1 to 28 of a 28-day cycle.
- Control (Placebo) Arm B: Placebo orally every 12 hours plus either anastrozole 1 mg or letrozole 2.5 mg orally every 24 hours on Days 1 to 28 of a 28-day cycle.

Blinded study drug is defined as LY2835219 or placebo. Study treatment is defined as blinded study drug and/or NSAI.

The specific NSAI (anastrozole or letrozole) administered to patients is determined by the investigator. Patients should remain on the same NSAI throughout the study. In exceptional cases, in the absence of evidence of PD, the investigator may discuss a change in NSAI with the Lilly CRP. NSAI is a co-administered standard-of-care treatment. The investigator should refer to the NSAI label (that is, Patient Information Leaflet, Package Insert, Summary of Product Characteristics). Table JPBM.9.1 shows the treatment regimens.

Table JPBM.9.1. Treatment Regimens/Dosing Schedule

Regimen	Period/Cycle	Dose Day
Experimental Arm A		
LY2835219	Treatment/28-day cycle	150 mg PO every 12 hours on Days 1-28[a]
Anastrozole or Letrozole	Treatment /28-day cycle	1 mg PO every 24 hours on Days 1-28[b] or 2.5 mg PO every 24 hours on Days 1-28[b]
Control (Placebo) Arm B		
Placebo	Treatment/28-day cycle	PO every 2 hours Days 1-28[a]
Anastrozole or Letrozole	Treatment /28-day cycle	1 mg PO every 24 hours Days 1-28[b] 2.5 mg PO every 24 hours on Days 1-28[b]

Abbreviations: ECG = electrocardiogram; PK = pharmacokinetic; NSAI = nonsteroidal aromatase inhibitor; PO = orally.

[a] On Cycle 1 Day 1 only, patients should take one single dose of blinded study drug and initiate chronic every-12-hours dosing on Cycle 1, Day 2.

[b] For PK and ECG purposes, NSAI should be administered at the same time (or up to 20 minutes after) the morning dose of blinded study drug through Cycle 4, Day 1. Subsequently, the interval between administration of blinded study drug and NSAI may be adjusted based on the judgment of the investigator.

The investigator or his/her designee is responsible for the following:

- explaining the correct use of the drugs and planned duration of each individual's treatment to the patient/site personnel/legal representative,
- verifying that instructions are followed properly,
- maintaining accurate records of study drug dispensing and collection (including the co-administered NSAI doses taken by the patient),
- and returning all unused medication supplied by Lilly to Lilly or its designee at the end of the study.

Note: In some cases, sites may destroy the material if, during the investigator site selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose of clinical trial materials.

Patients will be instructed to contact the investigator as soon as possible if they have a complaint or problem with the study drug so that the situation can be assessed.

9.2. Materials and Supplies

LY2835219 or placebo (blinded study drug) will be supplied as capsules for oral administration. Blinded study drug capsules should be stored according to the product label, and not opened,

crushed, or dissolved. Blinded study drug will be labeled according to the country's regulatory requirements.

Where required, letrozole and anastrazole will be supplied by Lilly and labeled according to country regulatory requirements. Letrozole and anastrazole should be stored according to the product label and will be provided as anastrazole 1-mg or letrozole 2.5-mg tablets.

Investigators should instruct patients to store the blinded study drug and NSAI in the original package provided and in a location inaccessible to children.

9.3. Method of Assignment to Treatment

Upon obtaining informed consent, site personnel should access the interactive web response system (IWRS) which will assign a patient number. Patients who meet all criteria for enrollment will be randomly assigned to receive either LY2835219 or placebo. Assignment to treatment groups will be determined by a computer-generated random sequence using the IWRS. Sites will be prompted to enter the specific NSAI at time of randomization.

Randomization will be stratified by the following: nature of disease (visceral metastases versus bone-only metastases versus other), and prior (neo)adjuvant endocrine therapy (aromatase inhibitor therapy versus other versus no prior endocrine therapy).

The IWRS will be used to assign LY2835219 or placebo and distribute NSAI supplied by Lilly. Site personnel will confirm that they have located the correct sstudy medication packages by entering a confirmation number found on the packages into the IWRS.

The period between randomization to blinded study drug and the first dose (Cycle 1, Day 1) should not exceed 7 days.

9.4. Selection and Timing of Doses

Blinded study drug will be taken orally every 12 (±2) hours on Days 1 through 28 of a 28-day cycle, for a total of 56 doses per cycle. During all cycles, blinded study drug should be taken at approximately the same times each day. If a patient misses or vomits a blinded study drug dose, that dose should be omitted.

Anastrozole or letrozole will be administered orally every 24 hours (±2) on Days 1 through 28 of a 28-day cycle for a total of 28 doses per cycle. For PK and electrocardiogram (ECG) purposes, anastrozole or letrozole should be administered at the same time as (or up to 20 minutes after) the morning dose of blinded study drug through Cycle 4, Day 1. Subsequently, the interval between admin stration of blinded study drug and anastrozole or letrozole may be adjusted based on the judgment of the investigator. If a patient misses or vomits an anastrozole or letrozole dose, tha dose should be omitted.

A cycle is defined as an interval of 28 days plus any subsequent delay prior to start of the next c cle. A delay in the start of a cycle due to holidays, weekends, bad weather, or other unforeseen circumstances will be permitted up to 7 days and not counted as a protocol deviation). For each 28-day cycle, a total of 56 doses of blinded study drug will be dispensed.

In exceptional cases, for planned delays (including but not limited to vacation or holidays), additional study treatment may be dispensed.

A patient may continue to receive study treatment until she meets 1 or more of the specified reasons for discontinuation (as described in Section 7.3.1).

9.4.1. Special Treatment Considerations

9.4.1.1. Dose Adjustments and Delays

Table JPBM.9.2. Toxicity Dose Adjustments and Delays of Blinded Study Drug for Study JPBM

Toxicity Type	Toxicity Profile and Severity	Dose Suspension	Dose Reduction
Hematologic Toxicity Section 9.4.1.1.3	Grade 3	Dose **MUST** be suspended until toxicity resolves to at least Grade 2.	Dose **MAY** be reduced by 1 dose level - investigator's discretion.
Hematologic Toxicity Section 9.4.1.1.3	Recurrent Grade 3	Dose **MUST** be suspended until toxicity resolvess to at least Grade 2.	Dose **MUST** be reduced by 1 dose level.
Hematologic Toxicity Section 9.4.1.1.3	Grade 4	Dose **MUST** be suspended until toxicity resolves to at least Grade 2.	Dose **MUST** be reduced by 1 dose level.
Hematologic toxicity: **Patient requires administration of blood cell growth factors** Sections 9.4.1.1.3 and 9.6.4	Regardless of severity (Growth factors use according to ASCO Guidelines)	Dose **MUST** be suspended for at least 48 hours after the last dose of blood cell growth factors was administered and until toxicity resolves to at least Grade 2	Dose **MUST** be reduced by 1 dose level unless already performed for incidence of toxicity that lead to the use of growth factor.
Nonhematologic Toxicity (except diarrhea) Section 9.4.1.1.4	Persistent or recurrent Grade 2 that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Dose **MAY** be suspended until toxicity resolves to either baseline or Grade 1.	Dose **MAY** be reduced by 1 dose level - investigator's discretion.
Nonhematologic Toxicity Section 9.4.1.1.4	Grade 3 or 4	Dose **MUST** be suspended until toxicity resolves to either baseline or Grade 1.	Dose **MUST** be reduced by 1 dose level.
Diarrhea Section 9.4.1.1.4.1	Requires hospitalization or Grade 3 or 4	Dose **MUST** be suspended until toxicity resolves to at least Grade 1.	Dose **MUST** be reduced by 1 dose level.
Diarrhea Section 9.4.1.1.4.1	Persistent or recurrent Grade 2 that does not resolve with maximal supportive measures within 24 hours to at least Grade 1	Dose **SHOULD** be suspended until toxicity resolves to at least Grade 1.	Dose **MAY** be reduced by 1 dose level - investigator's discretion.
Diarrhea Section 9.4.1.1.4.1	Diarrhea recurs despite maximal supportive measures after resuming same dose level after initial Grade 2 diarrhea	Dose **MUST** be suspended until toxicity resolves to at least Grade 1.	Dose **MUST** be reduced by 1 dose level.

Abbreviation: ASCO = American Society of Clinical Oncology.
Note: MAY = per the investigator's clinical judgment; SHOULD = not mandatory but highly recommended; MUST = mandatory.

9.4.1.1.1. Dose Adjustments

9.4.1.1.1.1. Blinded Study Drug

Blinded study drug dose adjustments as outlined in Table JPBM.9.3 are allowed both within a cycle and between cycles. Blinded study drug must be reduced sequentially by one dose level.

For patients requiring dose reduction(s), any re-escalation to a prior dose level is permitted only after consultation with the Lilly CRP.

Table JPBM.9.3. Dose Adjustments for Blinded Study Drug

Dose Adjustment Level	Oral Dose	Frequency
0	150 mg	Every 12 hours
1	100 mg	Every 12 hours
2	50 mg	Every 12 hours

Blinded study drug must be discontinued if further dose reduction is required b yond 50 mg every 12 hours. In the event that blinded study drug must be discontinued, a patient may continue to receive anastrozole or letrozole.

9.4.1.1.1.2. Anastrozole or Letrozole

Per NSAI labels, dose adjustment for anastrozole or letrozole is not applicable, as only a single-dose strength is approved for each medication. In exceptional cases in the absence of evidence of PD, the investigator may discuss a change in the specific NSAI administration (for example, switching from anastrozole to letrozole) with the Lilly CRP. In the event that anastrozole or letrozole must be discontinued,, a patient may continue to receive blinded study drug per the investigator's clinical judgment.

Dose Suspension (within a Cycle) and Cycle Delay

Both dose suspension (within a cycle) and cycle delay are permitted. When a dose suspension or cycle delay occurs related to toxicity (defined as an AE possibly related to study treatment per investigator judgment), the blinded study drug and/or NSAI may be suspended or delayed as determined by the investigator's judgment.

Study treatment may be h ld up to 14 days within a cycle or at start of next cycle to permit sufficient time for recovery from the toxicity. If a dose suspension occurs within a cycle, the investigator may resume blinded study drug dosing at the same dose level for the remainder of the cycle or at reduced dose (assuming resolution to at least Grade 1 for non-hematological and at least Grade 2 for hematological toxicity). If the patient experiences the same toxicity with the same or greater severity (CTCAE grade) requiring a dose suspension within a cycle or at start of the next cycle, the patient must be dose reduced and not re-challenged a second time at the prior dos level.

Patients not recovering from toxicity within 14 days should be considered for discontinuation of the blinded study drug and/or co-administered NSAI. In exceptional circumstances, a delay >14

days is permitted upon agreement between the investigator and the Lilly CRP and blinded study drug dose adjustment is to be considered.

In the event of a cycle delay due to logistical reasons (for example, due to patient availability), the patient should continue on study treatment if the patient has adequate drug supply. If a patient's treatment is interrupted as a result of not having sufficient drug supply, the cycle may be delayed up to 7 days (and not be considered a protocol violation). In exceptional circumstances, a delay >7 days is permitted upon agreement between the investigator and the Lilly CRP.

The start of a cycle may be delayed, or a current cycle interrupted, to allow a patient with a locoregionally recurrent breast cancer rendered operable by study treatment to receive surgery ± radiotherapy. For additional information, refer to Section 9.6.1.

- ***Hematologic Toxicity***

If a patient experiences Grade 4 hematologic toxicity, then dosing must be suspended (until the toxicity resolves to at least Grade 2) and the dose of blinded study drug must be reduced by one dose level as outlined in Table JPBM.9.3.

If a patient experiences Grade 3 hematologic toxicity, then dosing must be suspended (until the toxicity resolves to at least Grade 2) and the dose of blinded study d ug may be reduced by one dose level as outlined in Table JPBM.9.3 at the discretion of the investigator. If the patient experiences a recurrent episode of Grade 3 hematologic toxicity, then dosing must be suspended (until the toxicity resolves to at least Grade 2) and the dose of blinded study must be reduced by 1 dose level.

If a patient requires administration of blood cell growth factors, the dose of study drug must be suspended for at least 48 hours after the last dose of blood cell growth factors was administered and until toxicity resolves to at least Grade 2 then reduced by 1 dose level, if a dose reduction for the specific event necessitating the use of the growth factors has not already occurred.

Before the start of each cycle, hematologic toxicity must resolve to at least Grade 2.

- ***Nonhematological Toxicity***

If a patient experiences 2'Grade 3 nonhematologic toxicity, then blinded study drug and/or NSAI dosing must be suspended (until the toxicity resolves to either baseline or at least Grade 1) and the dose of blinded study drug must be reduced by one dose level as outlined in Table JPBM.9.3.

If a patient experiences persistent or recurrent Grade 2 nonhematologic toxicity (except diarrhea; refer to Section 9.4.1.1.4.1) that does not resolve with maximal supportive measures within 7 days to e ther baseline or at least Grade 1, then blinded study drug and/or NSAI dosing may be suspend d (until the toxicity resolves to either baseline or at least Grade 1) and the dose of blinded study drug may be reduced by one dose level as outlined in Table JPBM.9.3 at the discretion of the investigator.

Before the start of each cycle, nonhematologic toxicity (except alopecia and fatigue) must resolve to either baseline or at least Grade 1.

9.4.1.1.4.1. Diarrhea

A patient experiencing diarrhea requiring hospitalization (irrespective of grade, that is, requiring intravenous [IV] rehydration) or severe diarrhea (Grade 3 or 4; see Attachment 9) must have study treatment suspended (until the toxicity resolves to at least Grade 1) and must have the blinded study drug dose reduced by one dose level as outlined in Table JPBM.9.3.

If a patient experiences persistent or recurrent Grade 2 diarrhea that does not resolve with maximal supportive measures (refer to Section 9.6.5) within 24 hours to at least Grade 1, then study treatment should be suspended (until the toxicity resolves to at least Grade 1) and the dose of blinded study drug may be reduced by one dose level as outlined in Table JPBM.9.3 at the discretion of the investigator. If the same dose level was resumed and diarrhea recurs despite maximal supportive measures, the dose of blinded study drug must be reduced by one dose level as outlined in Table JPBM.9.3

9.5. Blinding

This is a double-blind study.

To preserve the blinding of the study, a minimum number of Lilly personnel will see the randomization table and treatment assignments before the study is complete. Access to unblinded data/documents will be controlled by restricting access to the data/documents in Lilly's data and statistical warehouse. Any changes to this unblinding plan may be described in a protocol amendment, the SAP, and/or a separate unblinding plan document.

Efficacy information will not be shared between sites until the study is completed. Upon overall study completion (see Section 8.1.1), investigators may unblind patients to study treatment assignment.

9.5.1. Unblinding at Interim Analyses

Interim analyses for safety and efficacy will be conducted, using unblinded data, under the guidance of an independent Data Monitoring Committee (DMC). The DMC will consist of at least 3 members, including at least 1 clinician and 1 statistician. The DMC will communicate any recommendations based on interim analysis to the Lilly Senior Management Designee (SMD). If necessary, the SMD may form an Internal Review Committee (IRC) to review and act upon the recommendations of the DMC. See Section 12.2.14 for details on the conduct of interim analyses.

9.5.2. Emergency Unblinding

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted. Patient safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is war anted, the investigator should make every effort to contact the Lilly CRP prior to unblinding a patient's treatment assignment unless this could delay emergency treatment of the patient. If a patient's treatment assignment is unblinded, Lilly must be notified immediately.

Emergency unblinding for AEs must be performed through the IWRS. This option may be used ONLY if the patient's acute well-being requires knowledge of the patient's treatment assignment or if a patient discontinues treatment due to disease progression based upon RECIST 1.1 (see Attachment 5) and knowledge of the patient's treatment assignment is deemed essential to the selection of the patient's next treatment regimen. In the case of disease progression, the investigator must consult with the Lilly CRP prior to unblinding.

All calls resulting in an unblinding event are recorded and reported by the IWRS. Iff the investigator or patient becomes unblinded, that patient will be discontinued from study treatment and will undergo postdiscontinuation follow-up (Attachment 1). Long-term follow up procedures will be followed until death or study completion.

9.5.3. Inadvertent Unblinding

Every effort will be made to blind both the patient and the investigator to the identity of the treatment, but the inadvertent unblinding of a patient may occur. A double-blind study design is known to be imperfect in the oncolytic setting because the potential for individual unblinding exists due to treatment-related signs and symptoms. If an investigator, site personnel performing assessments, or patient is unblinded, the unblinding will not be sufficient cause (in and of itself) for that patient to be discontinued from study therapy or excluded from any safety or efficacy analyses.

Additionally, there may be ethical reasonss to have the patient remain on the study treatment. For patients to continue on study treatment in the event of unblinding, the investigator must obtain specific approval from a Lilly CRP for the patient to continue in the study.

9.6. Concomitant Therapy

Appropriate documentation of all forms of premedications, supportive care, and concomitant medications must be captured at each visit in the eCRF. Concomitant medications and supportive care therapies must also be documented at the time of discontinuation and at the 30-day short-term follow-up visit.

With the exceptions listed in the sections below, therapies for cancer (including hormonal anticancer therapies, chemotherapy, and immunotherapy) will not be permitted while patients are on study treatment. Use of megestrol acetate as an appetite stimulant is not permitted.

The results from an in vitro human recombinant cytochrome P450 (CYP) phenotyping study indicate that oxidative metabolism of LY2835219 is primarily catalyzed by CYP3A.

Radiolabeled human disposition study indicates that LY2835219 is mostly cleared by oxidative metabolism and therefore inhibitors and or inducers of CYP3A may alter the metabolism of LY2835219. Based on these findings, grapefruit juice as well as inducers (for example, phenytoin or carbamazepine) and strong inhibitors of CYP3A should be substituted or avoided if possible (Attachment 8). All patients may receive supportive therapy with dexamethasone, preferably :S7 days, if clinically indicated. Patients requiring more than 7 days of dexamethasone therapy will not incur a protocol deviation.

In addition, in vitro studies in cultured human hepatocytes indicate that abemaciclib and its major metabolites LSN2839567 and LSN3106726 down regulate mRNA of 1 or more CYPs, including CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2D6, and CYP3A, at clinically relevant concentrations. The mechanism of down regulation and its clinical relevance are presently not understood. Therefore, care should be taken when coadministering substrate drugs of the above CYPs with narrow therapeutic margin (Attachment 8).

9.6.1. Surgery and/or Radiotherapy for Locoregionally Recurrent Breast Cancer

A patient with locoregionally recurrent breast cancer may receive surgery ± radiotherapy if study treatment renders the tumor operable. However, such a patient should not receive study treatment for the period beginning at least 7 days prior to surgery and continuing until at least 14 days after completion of surgery ± radiotherapy to allow for tissue healing and recovery. There is no restriction on the duration of this period without study treatment and, after this period ends, study treatment may resume. Importantly, a patient who receives surgery ± radiotherapy for locoregionally recurrent breast cancer is not considered noncompliant and does not incur a protocol deviation.

9.6.2. Radiotherapy

Except as described in Section 9.6.1, radiotherapy is not permitted without permanent discontinuation from study treatment. Except for a patient w th locoregionally recurrent breast cancer rendered operable by study treatment who subsequ ntly undergoes surgery + radiotherapy, all other patients requiring radiotherapy should discontinue permanently from study treatment and have a tumor assessment of the lesion(s) before receiving radiotherapy.

9.6.3. Supportive Care

Patients should receive full supportive car to maximize quality of life. Patients will receive supportive care as judged by their treating physician. If it is unclear whether a therapy should be regarded as supportive care, the investigator should consult the Lilly CRP. Use of any supportive care therapy should be reported on the eCRFs.

9.6.4. Growth Factors

Growth factors should not be administered to enable a patient to satisfy study inclusion criteria.

Growth factors may be administered in accordance with ASCO guidelines (Smith et al. 2015). Dosing of blinded study drug must be suspended if the administration of growth factors is required and must not be recommenced within 48 hours of the last dose of growth factors having been administered. Following the administration of growth factors, the dose of blinded study drug must be reduced by 1 dose level, if a dose reduction for the specific event necessitating the use of the growth factors has not already occurred.

9.6.5. Supportive Management for Diarrhea

At randomization, patients should receive instructions on the management of diarrhea. In the event of diarrhea, supportive measures should be initiated as early as possible. These include the following:

- At the first sign of loose stools, the patient should initiate anti-diarrheal therapy (e.g., loperamide) and notify the investigator for further instructions and appropriate follow-up.
- Patients should also be encouraged to drink fluids (e.g., 8 to 10 glasses of clear liquids per day).
- Site personnel should assess response within 24 hours.
- If diarrhea does not resolve with anti-diarrheal therapy within 24 hours to at least Grade 1, blinded study drug should be suspended until diarrhea is resolved to at least Grade 1.
- When blinded study drug recommences, dosing should be adjusted as outlined in Section 9.4.1.1.4.1 and Table JPBM.9.3.

In severe cases of diarrhea, the measuring of neutrophil counts and body temperature and proactive management of diarrhea with antidiarrheal agents should be considered.

If diarrhea is severe (requiring IV rehydration) and/or associated with fever or severe neutropenia, broad-spectrum antibiotics such as fluoroquinolones must be prescribed.

Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting should be carefully monitored and given intravenous fluid (IV hydration) and electrolyte replacement.

9.6.6. Bisphosphonates and RANK-L Targeted Agents

Patients with bone metastases present on baseline imaging should be appropriately treated with bisphosphonates or RANK-L targeted agents (for example, denosumab), per respective approved labels. Initiation of treatment with bone-modifying agents must begin at least 7 days prior to randomization. Patients receiving bisphosphonates or RANK-L targeted agents should not switch treatments (for example, replace a bisphosphonate with denosumab) while on study treatment. However, exceptional cases without evidence of PD may be considered in consultation with the Lilly CRP. These exceptional cases will not incur a protocol deviation.

9.7. Treatment Compliance

Treatment compliance information for study treatment will be collected through patient dosing diaries and/or capsule/tablet counts at each visit, with the number of capsules/tablets taken relative to the number expected to be taken summarized for each cycle. The patient must take 2'75% of the planned doses for study treatment in a cycle to be deemed compliant. As outlined in Section 9.4.1.1.2, dose suspensions or delays may occur and will not result in a patient being conssidered as noncompliant. A patient may be considered noncompliant if she is judged by the investigator to have intentionally or repeatedly taken 2'125% of the planned doses of study treatment in a cycle.

Importantly, a patient who receives surgery ± radiotherapy for locoregionally recurrent breast cancer is not considered noncompliant and does not incur a protocol deviation. For additional information, refer to Section 9.6.1.

Potential discontinuation of a patient due to study drug noncompliance will be discussed between the investigator and the Lilly CRP before any determination is made to discontinue the patient.

9.7.1. Patient Diaries

The study will include patient diaries to provide dosing instructions, help patients with treatment planning, and track actual doses of study treatment taken by the patient. Information from the diaries may be used for documenting study treatment compliance as well as dosing time relative to PK blood draws and ECG collection.

10. Efficacy, Health Outcome/Quality-of-Life Measures, Safety Evaluations, Sample Collection and Testing, and Appropriateness of Measurements

Written informed consent must be obtained prior to any study-specific pretreatment evaluations.

Study procedures related to efficacy, safety, health outcome/quality-of-life measures, sample collection and testing assessments and their timing are described in the sections below and shown in the Study Schedule (Attachment 1).

10.1. Efficacy Measures

10.1.1. Efficacy Assessments at Baseline and durring Study Treatment

Within 28 days of randomization, baseline tumor assessments will beperformed for each patient. The method of assessment used at baseline must be used consistently for serial tumor assessment throughout the study. Bone scintigraphy will be performed for all patients at baseline (within 28 days of randomization). However, prior bone scintigraphy (obtained as pa t of routine clinical care) within 45 days before Day 1 of Cycle 1 is also acceptable. All tumor assessment images must be submitted for central review.

For all patients, imaging studies (computed tomography [CT], including spiral CT, or magnetic resonance imaging [MRI] scan of the chest, abdomen, and pelvis) will be performed locally at baseline and repeated between Day 21 and Day 28 of eve y second cycle beginning with Cycle 2 and continuing through Cycle 18 (inclusive), between Day 21 and 28 of every third cycle after Cycle 18, and within 14 days of clinical progression per the Study Schedule (Attachment 1). It is recommended that CT imaging of the abdomen and pelvis be performed with IV contrast, whenever possible. For patients with known hypersensitivity to CT contrast material, a CT scan of the chest without contrast and gadolinium-enhanced MRI of the abdomen and pelvis are encouraged. The CT portion of a positron emission tomography (PET)-CT scan may be used as a method of response assessment if the site can document that the CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast). A PET scan alone or as part of a PET-CT may be performed as part of r utine clinical care but cannot be used to assess response according to RECIST v1.1.

For all patients, bone scintigraphy will be performed locally at baseline and repeated between Day 21 and Day 2 of every sixth cycle beginning with Cycle 6. In addition, bone scans should be repeated even if a complete response in target disease is identified or progression in bone is suspected. For patients with new lesions identified by post-baseline bone scintigraphy, targeted assessment by X-ray, CT scan with bone windows, or MRI will be performed to confirm findings.

F r only those patients with bone lesions identified by bone scintigraphy at baseline, directed imaging using one of the following methods will be performed at baseline: X-ray, CT scan with bone windows, or MRI. Directed imaging using the same method as at the baseline bone lesion

assessment should be repeated between Day 21 and Day 28 of every second cycle beginning with Cycle 2 and continuing through Cycle 18 (inclusive), between Day 21 and Day 28 of every third cycle after Cycle 18, and within 14 days of clinical progression.

For patients with locoregionally recurrent breast cancer not amenable to curative treatment, MRI scan of the breast will be performed at baseline, if applicable. Breast MRI, if applicable, will be repeated between Day 21 and Day 28 of every second cycle beginning with Cycle 2 and continuing through Cycle 18 (inclusive), between Day 21 and Day 28 of every third cycle after Cycle 18, and within 14 days of clinical progression.

For patients with visible tumor (such as skin lesions), photography will be performed at baseline and each photographic image of the tumor should include a ruler. Photography should be repeated on Day 1 of every second cycle beginning with Cycle 3 and continuing through C cle 19 (inclusive), on Day 1 of every third cycle after Cycle 19, and within 14 days of clini al progression. Photographic images may be taken more frequently based upon the dis retion of the investigator or following the identification of new skin lesions post-baseline.

For patients continuing treatment during the Continued Access Period (after study completion), efficacy assessments (frequency and type of assessments) will be at the discretion of the investigator.

10.1.2. Efficacy Assessments during Postdiscontinuation Follow-Up

Postdiscontinuation follow-up during the study period will be conducted as described in the Study Schedule (Attachment 1).

For those patients who are randomized and never receive study treatment or those who discontinue study treatment without objectively m asured PD, the investigative sites will continue to monitor patients and periodically evaluate tumor response approximately every 8 weeks for the first 18 months following randomization and thereafter approximately every 12 weeks by the same method used at baseline and throughout the study until the patient has objective disease progression, or until the final analysis of PFS. In addition, anticancer therapies initiated after study treatment discontinuation will be collected during this follow-up period. After the patient has objective disease progression, radiologic imaging and photographic images are no longer required and the patient will be followed up approximately every 12 weeks until the patient's death or overall study completion.

Lilly will continue to collect survival data on all patients but may reduce data collection for other efficacy data. Lilly will notify investigators when this reduced data collection can begin.

10.1.3. Primary Efficacy Measure

The primary efficacy measure is PFS as defined by [RECIST v1.1 (Eisenhauer et al. 2009)] provided in Attachment 5.

Lilly or its designee will collect and store all tumor assessment images on all enrolled patients throughout the study. An independent review of a randomly selected subset of patient scans will be performed by independent panel of radiologists (Section 12.2.8).

The PFS time is measured from the date of randomization to the date of objective progression or the date of death due to any cause, whichever is earlier.

For those patients with nonmeasurable, bone-only disease (refer to Inclusion Criterion [4]), objective progression will be established if at least 1 of the following criteria is met:

- the appearance of 1 or more new lesions (in bone or outside of bone), or
- unequivocal progression of existing bone lesions.

According to RECIST v1.1, the finding of a new lesion should be unequivocal and not attributable to findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of preexisting lesions). Pathologic fracture, new compression fracture, or complications of bone metastases will not be considered as evidence of disease progression, unless at least 1 of the above criteria is met.

For those patients with locoregionally recurrent disease for whom surgery is performed with no evidence of residual disease post-operatively, objective progression will be established if at least 1 of the following criteria is met:

- local and/or regional recurrence, or
- new development of metastatic disease.

For those patients with locoregionally recurrent disease for whom surgery is performed while on study with evidence of residual disease post-operatively, new baseline measurements should be taken and RECIST applied.

If a patient is not known to have progressed or died at the time of analysis, PFS time will be censored at the last known progression-free assessment. See Section 12.2.6 for detailed censoring rules.

10.1.4. Secondary Efficacy Measures

The following secondary efficacy measures (Table JPBM.10.1) will be collected at the times shown in the Study Schedule (Attachment 1).

Table JPBM.10.1. Secondary Efficacy Endpoints

Endpoint	Definition
Overall Survival (OS)	The time from the date of study randomization to the date of death from any cause
Objective Response Rate	The proportion of patients with CR or PR according to RECIST v1.1
Disease-Control Rate (DCR)	The proportion of patients with CR, PR, or SD according to RECIST v1.1
Clinical Benefit Rate (CBR)	The proportion of patients with CR, PR, or SD 2'6 months according to RECIST v1.1
Duration of Response (DoR)	The time from the date of first evidence of a confirmed CR or PR to the date of objective progression (according to RECIST v1.1) or death from any cause, whichever is earlier

Abbreviations: CR = complete response; PR = partial response; PS = performance status; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.

Overall Survival (OS): OS duration is measured from the date of randomization of any study drug to the date of death from any cause. For each patient who is not known to have died as of the data-inclusion cutoff date for a particular analysiiss,, OS will be censored for that analysis at the last known alive date.

Objective Response Rate (ORR): The objective response rate is the percentage of patients with a best response of CR or PR.

Duration of Response (DoR): The DoR time is defined only for responders (patients with a confirmed CR or PR). It is measured from the date of first evidence of CR or PR to the date of objective progression or the date of death due to any cause, whichever is earlier. For clarity, the start date should be determined by the initial assessment of CR or PR, not the date of confirmation of CR or PR. If a responder is not known to have died or have objective progression as of the data inclusion cutoff date scores, DoR will be censored at the last complete objective progression-free disease assessment date.

Disease Control Rate (DCR): The DCR is the percentage of patients with a best response of CR, PR, or SD.

Clinical Benefit Rate (CBR): The CBR is the percentage of patients with a best response of CR or PR, or SD for at least 6 months.

10.1.5. Exploratory Measures

Table JPB .10.2. Exploratory Measures

Biomark rs	Potential biomarkers related to the mechanism of action of LY2835219, the cell cycle, and/or the pathogenesis of breast cancer
CTS (change in tumor size)	Change in the size of target lesions

Biomarkers: Exploratory analysis using blood and tumor tissues will be done to explore potential biomarkers related to the mechanism of action of LY2835219, the cell cycle, and/or the pathogenesis of breast cancer to better understand relationships of cellular signaling defects with clinical outcomes.

Change in Tumor Size: Change in tumor size will be measured using target lesion measurements selected for radiological evaluation. This measurement will only be available on patients with measureable disease.

10.2. Health Outcome/Quality-of-Life Measures

10.2.1. Patient-Reported Outcomes

The primary health outcomes research goal is to assess if LY2835219 combination therapy is able to impact the quality of life, as measured by the EORTC QLQ-C30 (Aaronson et al. 1993). Additionally, the EORTC QLQ-BR23 (Sprangers et al. 1996) will collect disease-specific data, and the EQ-5D 5L (Janssen et al. 2008) health status assessment will allow for comparison with other tumor types and disease states.

Patient-reported questionnaires should be completed by patients when a language translation is available in which the patient is fluent or literate.

At each time point identified in the Study Schedule (Attachment 1), a paper copy of the EQ-5D 5L, EORTC QLQ-C30 and EORTC QLQ-BR23 questionnaires should be administered to the patient prior to extensive interaction with site staff and study drug administration.

10.2.1.1. Health-Related Quality of Life

Broadly used in cancer trials, validated, and available in over 80 different languages, the EORTC QLQ-C30 (Aaronson et al. 1993) is a reliable and validated tool. The EORTC QLQ-C30 self-reported general cancer instrument consists of 30 items covered by 1 of 3 dimensions:

- global health status/quality of life (2 items)
- functional scales (15 total items addressing either physical, role, emotional, cognitive, or social functioning)
- symptom scales (13 total items addressing either fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, or financial impact)

The EORTC QLQ-BR23 (Sprangers et al. 1996) consists of 23 items covered by the following scales:

- functional (body image and sexuality)
- symptom scales (arm, breast, and systemic therapy side effects)

The EORTC QLQ-C30 and EORTC QLQ-BR23 questionnaires are administered per the Study Schedule (Attachment 1). The recall period is the past week, completion time is typically 5 to 7 minutes, and both questionnaires will be scored as described by the EORTC scoring manual (Fayers et al. 2001).

10.2.1.2. Health Status

The EQ-5D 5L (Janssen et al. 2008) is a standardized instrument for use across diseases as a measure of self-reported health status. Specifically, this questionnaire is included in this trial to evaluate health-state utilities associated with advanced breast cancer. These utility measures are an important input for economic evaluations concerning the value of treatment interventions.

The EQ-5D 5L is designed to be used in conjunction with other patient-reported measures. Patients will complete the 5-dimension (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), 5-level (no problem, slight, moderate, severe, or extreme problem) assessment according to the Study Schedule (Attachment 1). A visual analog scale (VAS) "thermometer" measures current health state. Additionally, EQ-5D 5L responses may be incorporated into cost utility analyses.

Administration is preferably scheduled after the EORTC and before extensive contact with study personnel or clinicians, which could result in biased patient response. The recall period is "today." The EQ-5D 5L is designed for self-completion by respondents and is cognitively simple, taking only a few minutes to complete.

10.2.2. Resource Utilization

Investigators will be asked to report the use of concomitant medications (in particular, analgesics, bisphosphonates, and RANK-L targeted agents), blood product transfusions, radiation therapy, surgery, and hospitalization days. Data on neurosurgical blocks will be recorded on the Concomitant Medication and/or surgery eCRF as appropriate. This information should be collected during the study and at the 30-day follow-up visit.

10.3. Safety Evaluations

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient.

The investigator is responsible for the appropriate medical care of patients during the study.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious, considered related to the study, or that caused the patient to discontinue before completing the study. The patient should be followed until the event is resolved or explained. Frequency of follow-up evaluation is left to the discretion of the investigator.

The timing of all safety evaluations is shown in the Study Schedule (Attachment 1). Table JPBM.10.3 presents a summary of AE and SAE reporting guidelines and also shows which database or system is used to store AE and SAE data.

Table JPBM.10.3. Adverse Event and Serious Adverse Event Reporting Guidelines

Period	Types of AEs/SAEs to be Reported	Collection Database	Lilly Safety System
Baseline (pretreatment)	Preexisting conditions	x	
	All AEs	x	
	SAEs related to protocol procedures	x	x
Study treatment period	All AEs	x	
	All SAEs	x	x
30-day short-term postdiscontinuation follow-up	All AEs	x	
	All SAEs	x	x
Long-term postdiscontinuation follow-up	All SAEs related to protocol procedures or study drug	x	x
Continued access period	All AEs	x	
	All SAEs	x	x
Continued access period follow-up	All AEs	x	
	All SAEs	x	x
After the patient is no longer participating in the study (that is, no longer receiving study therapy and no longer in follow-up)	All SAEs related to protocol procedures or study drug that the iinvestigator becomes aware of		x

Abbreviations: AEs = adverse events; SAEs = serious adverse events.

10.3.1. Adverse Events

Lilly has standards for reporting AEs that are to be followed regardless of applicable regulatory requirements that may be less stringent. A clinical study AE is any untoward medical event associated with the use of a drug in humans, whether or not it is considered related to that drug.

Lack of drug effect is not an AE in clinical trials, because the purpose of the clinical trial is to establish drug effec .

Any clinically significant findings from ECGs, labs, vital sign measurements, and other procedures that result in a diagnosis should be reported to Lilly or its designee.

Study ssite personnel will record the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in tthe study.

After the ICF is signed, site personnel will record the occurrence and nature of any AEs and any change in the preexisting condition(s). All AEs related to protocol procedures are reported to Lilly or its designee.

Investigators will be instructed to report to Lilly or its designee their assessment of the potential relatedness of each AE to protocol procedure and study drug via eCRF.

The investigator will decide whether he or she interprets the observed AEs as related to disease, to the study medication, study procedure, or other concomitant treatment or pathologies. To assess the relationship of the AE to the study drug or procedure, the following terminologies are defined:

- **Probably related**: a direct cause and effect relationship between the study treatment and the AE is likely
- **Possibly related**: a cause and effect relationship between the study treatment and the AE has not been demonstrated at this time and is not probable, but is also not impossible
- **Does not know:** the investigator cannot determine
- **Not related**: without question, the AE is definitely not associated with the study treatment

The investigator should classify all "probably related," "possibly related," or "does not know" AEs and SAEs as related to study drug/study procedure.

Patients will be evaluated for AEs at each visit and will be instructed to call their physician to report any AEs between visits.

The National Cancer Institute (NCI)-CTCAE v 4.0 will serve as the reference document for choosing appropriate terminology for, and grading the severity of, all AEs and other symptoms. For AEs without matching terminology within the NCI-CTCAE v 4.0 criteria, the investigator will be responsible for selecting the appropriate system organ class and assessing severity grade based on the intensity of the event.

In addition to collecting the AE verbatim and the CTCAE severity grade, AE verbatim text will also be mapped by Lilly or its designee to corresponding terminology within the Medical Dictionary for Regulatory Activities (MedDRA) dictionary.

If a patient's dosage is reduced or treatment is discontinued as a result of an AE, study site personnel must clearly report to Lilly or its designee via eCRF the circumstances and data leading to any such dosage reduction or discontinuation of treatment.

10.3.1.1. Serious Adverse Events

An SAE is any AE from this study that results in one of the following outcomes:

- death
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- initial or prolonged inpatient hospitalization
- congenital anomaly/birth defect

- considered significant by the investigator for any other reason

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug events when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Serious adverse event collection begins after the patient has signed informed consent and has received study drug. If a patient experiences an SAE after signing informed consent, but prior to receiving study drug, the event will not be reported as serious unless the investigator feels the event may have been caused by a protocol procedure.

Data on SAEs that occur before the end of trial will be stored in the collection database and the Lilly Safety System.

Study site personnel must alert Lilly or its designee of any SAE within 24 hours of iinvestigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms.

This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

Planned surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study.

Planned hospitalizations or procedures for preexisting conditions that are already recorded in the patient's medical history at the time of study enrollment should not be considered SAEs. Hospitalization or prolongation of hospitalization without a precipitating clinical AE (for example, for the administration of study therapy or other protocol-required procedure) should not be considered SAEs.

Serious adverse events due to disease progression, including death, should not be reported unless the investigator deems them to be possibly related to the study drug.

If an investigator becomes aware of an SAE occurring after the patient's participation in the trial has ended, and the investigator believes that the SAE is related to a protocol procedure or study drug, the investigator should report the SAE to the sponsor, and the SAE will be entered in the Lilly Safety System.

Information on SAEs expected in the study population independent of drug exposure and that will be assessed by the sponsor in aggregate periodically during the course of the trial may be found in the IB.

10.3.1.2. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed iinthe Development Core Safety Information (DCSI) in the IB and that the investigator identifies as related to the study drug or study procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national

regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and associated detailed guidances.

10.3.2. Other Safety Measures

10.3.2.1. Electrocardiograms

For each patient, 12-lead digital ECGs will be collected according to the Study Schedule (Attachment 1). Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. Electrocardiograms may be obtained at additional times, if clinically indicated.

Electrocardiograms will be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the patient is still present for immediate patient management, should any clinically relevant findings be identified.

After enrollment, if a clinically significant increase in the QT/corrected QT (QTc) interval from baseline, or other clinically significant quantitative or qualitative change from baseline, is present, the investigator will assess the patient for symptoms (for example, palpitations, near syncope, syncope) and to determine if the patient can continue in the study. The investigator or qualified designee is responsible for determining if any change in patient management is needed and must document his/her review of the ECG printed at the time of evaluation.

10.3.3. Safety Monitoring

The Lilly CRP will monitor safety data throughout the course of the study.

Lilly will review SAEs wiitthin time frames mandated by company procedures. The Lilly CRP will, as is appropriate, consult with the functionally independent Global Patient Safety therapeutic area physician or clinical scientist, and review:

- trends in safety data
- laboratory analytes
- AEs
- if a patient experiences elevated ALT or AST >5x ULN in the absence of liver metastases and elevated total bilirubin >2x ULN, clinical and laboratory monitoring should be initiated by the investigator. For patients entering the study with ALT or AST >3x ULN in the presence of liver metastases, monitoring should be triggered if ALT or AST is elevated to >2x baseline.
- details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. To ensure patient safety and comply with regulatory guidance, the investigator is to consult with the Lilly CRP regarding collection of specific recommended clinical information and follow-up laboratory tests. See Attachment 3.

In the event that safety monitoring uncovers an issue that needs to be addressed by unblinding at the group level, only members of the DMC (an advisory group for this study formed to protect the integrity of data; refer to Section 12.2.14) can conduct additional analyses of the safety data.

For the purpose of this study, in which survival is a key efficacy endpoint, all deaths and SAE reports will be reviewed in a blinded manner by Lilly during the clinical trial. These reports will be reviewed to assure completeness and accuracy but will not be unblinded to Lilly during the clinical trial. If a death or other clinical AE is deemed serious, unexpected, and possibly related to study drug, only Lilly GPS representatives external to the study team will be unblinded for regulatory reporting and safety monitoring purposes. These measures will preserve the integrity of the data collected during this trial and minimize any potential for bias while providing for appropriate safety monitoring.

10.3.4. Complaint Handling

Lilly collects product complaints on study treatment used in clinical trials in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

All product complaints associated with material packaged, labeled, and released by Lilly or its designee will be reported directly to Lilly.

The investigator or his/her designee is responsible for handling the following aspects of the product complaint process in accordance with the instructions provided for this study:

- recording a complete description of the product complaint reported and any associated AEs using the study-specific complaint forms provided for this purpose
- faxing the completed product complaint form within 24 hours to Lilly or its designee

If the investigator is asked to return the product for investigation, he/she will return a copy of the product complaint form with the product.

10.4. Sample Collection and Testing

Attachment 1 lissttss the schedule for s mple collections in this study.

Attachment 2 lists the specific tests that will be performed for this study and whether these will be performed at a central or local laboratory.

Attachment 6 provides a summary of the estimated maximum number and volume of invasive samples, for all sampling, during the study.

Attachment 7 lliissts the schedule for PK sampling during the study.

10.4.1. Samples for Study Qualification and Health Monitoring

Blood samples will be collected to determine whether patients meet inclusion/exclusion criteria and to monitor patient health. Enrollment and treatment decisions may be based upon results of ttests performed locally. If local laboratory tests are used for this purpose, then a duplicate specimen must be submitted to the central laboratory. Discrepancies between local and central laboratory that may have an impact on eligibility or treatment decisions will not be considered

protocol deviations. In addition to protocol-specified tests, investigators should consider monitoring of cholesterol and bone mineral density if needed, per the recommendations for anastrozole and letrozole in the Package Insert and Summary of Product Characteristics.

Investigators must document their review of each laboratory safety report.

Samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Tests are run and confirmed promptly whenever scientifically appropriate. When scientific circumstances warrant, however, it is acceptable to retain samples to batch the tests run, or to retain the samples until the end of the study to confirm that the results are valid. Certain samples may be retained for a longer period, if necessary,, to comply with applicable laws, regulations, or laboratory certification standards.

10.4.2. Samples for Biomarkers

Samples for biomarker research to be collected from all patients in this study are the following:

- whole blood
- plasma
- tumor tissue

Analyses may include, but are not limited to, nucleic acid and protein profiles to better understand the disease process and to develop predictive biomarkers.

These samples are described in the following sections.

10.4.2.1. Archived Tumor Tissue

For patients in the study, a small amount of preserved tumor tissue, previously taken to evaluate the patient's disease, is required to be provided by sites upon patient randomization for biomarker research. However, if this sample is not available for a patient or the patient declines, a protocol deviation will not be incurred and the patient is eligible for the study.

Available formalin-fixed, paraffin-embedded primary and/or metastatic tumor tissue should be in a whole block, partial block, or unstained slides. Any whole block submitted will be returned to the site. Any partial blocks or sslides will either be returned or discarded within 15 years after last patient visit for the trial.

In tumor tissue samples, the CDK4 and CDK6 pathway components (for example, Rb) and markers relevant to breast cancer pathogenesis may be evaluated to assess any potential correlation with rresponse to LY2835219. Tumor samples may be analyzed to explore potential tumor gene signature(s) associated with response or resistance to LY2835219 therapy. These studies may be analyzed at a laboratory designated by the sponsor and may include IHC of proteins, FISH for copy number amplifications, RNA gene-expression profiling, and/or genetic analyses of the tumor specimen DNA. Such analyses may employ targeted or high-throughput sequencing approaches. For this purpose, the results of this analysis will be correlated with clinical efficacy data.

10.4.2.2. Blood Samples for Pharmacogenetic Evaluations

There is growing evidence that genetic variation may impact a patient's response to therapy. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion, the mechanism of action of the drug, the disease etiology and/or the molecular subtype of the disease being treated. Therefore, where local regulations and ethical review boards (ERBs) allow, a blood sample will be collected forr pharmacogenetic analysis.

Samples may be genotyped and analysis may be performed to evaluate a genetic association with response to LY2835219. These investigations may be limited to a focused candidate gene study or, if appropriate, genome-wide analysis may be performed to identify regiions of the genome associated with the variability observed in drug response. The pharmacogenetic biomarker samples will only be used for investigations related to disease and drug or class of drugs under study in the context of this clinical program. They will not be used for broad exploratory unspecified disease or population genetic analysis.

The samples will be coded with the patient number and stored for up to a maximum 15 years after the last patient visit for the study at a facility selected by the sponsor. The samples and any data generated from them can only be linked back to the patient by investigator site personnel. The duration allows the sponsor to respond to regulatory requests related to the study drug.

Samples will be destroyed according to a prrocess consistent wiitth local regulation.

10.4.2.3. Plasma Samples for Exploratory Biomarker Evaluations

EDTA-anticoagulated plasma samples will be collected and analysis may be performed on biomarkers that may play a role in the LY2835219 mechanism of action (refer to Attachment 1). The evaluation of these samples may involve analysis of DNA, RNA, and proteins (including any of these components derived from exosomes) to investigate their association with observed clinical outcomes to study drug. The samples will be coded with the patient number and stored for up to a maximum 15 years. Details fforcollecting, processing, and storing the samples are similar those provided in Section 10.4.2.2.

10.4.3. Samples for Drug Concentration Measurements Pharmacokinetics

At the visits and times specified in the Pharmacokinetic Sampling Schedule (Attachment 7), venous blood samples will be collected from at least 150 of the patients randomized in the study. These samples will be used to determine the plasma concentrations of LY2835219 and possibly LY2835219 m tabolites, as well as plasma concentrations of anastrozole or letrozole.

Instructions for the collection and handling of blood samples will be provided by the sponsor. It is preferred that the blood samples be obtained from a peripheral location. Blood samples will be allowed from central access devices, but a sample drawn from a central catheter of any type for PK must take precautions to prevent obtaining a dilute sample. If multiple samples are obtained centrally, the PK sample should be the last specimen drawn to reduce the potential for a diluted or improperly drawn sample. The actual date and time (24-hour clock time) of each

sampling will be recorded. A maximum of 5 samples may be drawn at additional time points during the study if warranted and agreed upon between both the investigator and Lilly.

These samples will be analyzed at a laboratory designated by the sponsor. Plasma concentrations of LY2835219 plus its metabolites LSN2839567, LSN3106726, and LSN3106729 will be assayed using a validated liquid chromatography/tandem mass spectrometry (LC/MS/MS) method. Plasma concentrations of anastrozole or letrozole will also be analyzed using a validated LC/MS/MS method. Bioanalytical samples collected to measure study drug concentration and metabolism and/or protein binding, will be retained for a maximum of 1 year following last patient visit for the study. The PK samples will be stored at a facility designated by the sponsor.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

10.5. Appropriateness of Measurements

Efficacy measurements by radiographic imaging are standard, widely used, and generally recognized as reliable, accurate, and able to discriminate between effective and ineffective agents.

Safety measurements by laboratory monitoring are standard, widely used, and generally recognized as reliable, accurate, and able to discriminate between agents with acceptable and unacceptable safety profiles.

11. Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- provide instructional material to the study sites, as appropriate
- sponsor start-up training to instruct the investigators and study coordinators. This session will give instruction on the protocol, the completion of the eCRFs, and study procedures.
- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- review and evaluate eCRF data and use standard computer edits to detect errors in data collection
- conduct a quality review of the database

In addition, Lilly or its representatives will periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Lilly or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

To ensure the safety of participants in the study, and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study. If requested, the investigator will provide Lilly, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

11.1. Data Capture System

An electronic data capture system will be used in this trial. The site maintains a separate source for the data entered by the site into the spons r-provided electronic data capture system.

Case report form data will be encoded and stored in a clinical trial database.

Any data for which the paper documentation provided by the patient will serve as the source document willll be identified and documented by each site in that site's study file.

Bioanalytical data will be stored electronically in the bioanalytical laboratory's database. Data will subsequently be transferred from the bioanalytical laboratory to Lilly.

Data from complaint forms submitted to Lilly will be encoded and stored in the global product complaint management system.

12. Sample Size and Statistical Methods

12.1. Determination of Sample Size

The primary objective of this study is to compare LY2835219 plus NSAI versus placebo plus NSAI in terms of PFS in postmenopausal women with HR+, HER2- locoregionally recurrent or metastatic breast cancer who have not received prior endocrine therapy in this disease setting.

The study will enroll approximately 450 patients in 2:1 randomization (300 patientss in LY2835219 plus NSAI and 150 patients in placebo plus NSAI). Patients will be randomized using the following stratification factors: nature of disease (visceral metastases versus bone-only metastases versus other) and prior (neo)adjuvant endocrine therapy (aromatase inhibitor thera y versus other versus no prior endocrine therapy).

A 3-look group-sequential design of the primary endpoint will be used to accommodate an event-driven plan for the interim and final PFS analyses (see Section 12.2.6 for details). The final PFS analysis will be performed after approximately 270 PFS events have occurred (that is, a 40% censoring rate). Assuming a hazard ratio of 0.67, this sample size yields more than 80% statistical power to detect superiority of the LY2835219 plus NSAI arm over the placebo plus NSAI arm with the use of a 1-sided log-rank test and a cumulative type I error of 0.025. If the true median PFS for the placebo plus NSAI arm is 10 months, then the hazard ratio of 0.67 amounts to an approximately 5-month (50%) improvement in median PFS for the LY2835219 plus NSAI arm under an additional assumption of exponential survival distribution.

12.2. Statistical and Analytical Plans

12.2.1. General Considerations

Statistical analysis of thiss study will be the responsibility of Lilly.

Efficacy analyses will be based on the i tention-to-treat (ITT) analysis set. This population is defined as all patients randomized to study treatment. Patients will be grouped according to randomized treatment.

Safety analyses will be based on the randomized and treated population (RT), defined as all randomized patients receiving at least 1 dose of blinded study drug or NSAI. Patients will be grouped according to treatment received in Cycle 1.

Pharmacodynamic and/or biomarker analyses will be based on the subset of patients from the above populations from whom a valid assay result (according to laboratory guideline) has been obtained.

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, unless otherwise stated. All confidence intervals (CIs) will be given at a 2-sided 95% level, unless otherwise stated.

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol.

Before sponsor unblinding of the aggregate database, minor modifications or clarifications to the data analysis methods may be described and justified in the statistical analysis plan.

Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report.

The assumptions for each statistical method may be evaluated. If there is violation of assumptions, alternative statistical methods may be used.

Additional exploratory analyses of the data will be conducted as deemed appropriate.

12.2.2. Patient Disposition

A detailed description of patient disposition will be provided. It will include a summary of the number and percentage of patients entered into the study, enrolled in the study, and treated, as well as number and percentage of patients completing the study or discontinuing (overall and by reason for discontinuation).

A summary of all important protocol deviations will be provided.

12.2.3. Patient Characteristics

Patient characteristics will include a summary by treatment arm of the following:

- patient demographics
- baseline disease characteristics
- preexisting conditions
- historical illnesses
- prior (neo)adjuvant endocrine therapy
- prior (neo)adjuvant chemotherapy (including both cytotoxic and targeted agents)

Other patient characteristics will be summarized as deemed appropriate.

12.2.4. Concomitant Therapy

Concomitant medications will be summarized by treatment arm.

12.2.4.1. Postdiscontinuation Therapy

The numbers and percentages of patients reporting postdiscontinuation therapies will be provided overall, by type of therapy (surgery, radiotherapy, or systemic therapy), and by drug name.

12.2.5. Treatment Compliance

The number of dose omissions, reductions, delays, the number of cycles received, and dose intensity will be summarized for all treated patients per treatment arm.

Compliance information for blinded study drug will be collected through capsule counts at each cycle/visit. The estimate of percent compliance will be given by:

$$\text{Percent Compliance} = \frac{\text{Actual cumulative dose taken}}{\text{Expected cumulative dose to be taken}} \text{ x } 100$$

The actual cumulative dose taken will be determined based on counting the number of capsules returned at each visit and subtracting that number from the number of capsules dispensed. The expected cumulative dose to be taken will be determined based on the assigned dose and taking into account any dose reductions or suspensions.

Compliance information for anastrozole or letrozole will be collected at each cycle/visit. This may be collected by tablet counts and/or review of the completed patient diary. For NSAI that has been centrally supplied by Lilly, tablet counts are required. The estimate of percent compliance will be done using the same formula/calculation for blinded study drug percent compliance.

12.2.6. Primary Outcome and Methodology

The primary endpoint of this study is PFS. PFS time is measured from randomization until the date of investigator-determined objective progression as defined by RECIST v1.1, or death from any cause. Patients who have neither progressed nor died will be censored at the day of their last radiographic tumor assessment, if available, or date of randomization if no post-initiation (that is, post-baseline) radiographic assessment is available. The detailed censoring rules are described in Table JPBM.12.1.

Table JPBM.12.1. Rules for Determining Date of Progression or Censor for Progression-Free Survival

Rule	Situation	Date of Progression or Censor	Outcome
1	No baseline tumor assessments	Date of Randomization	Censored
2	No post-baseline assessments and no death	Date of Randomization	Censored
3	No documented progression and no death (with a post-baseline tumor assessment)	Date of last adequate tumor assessment	Censored
4	Patient lost to follow-up (or withdrew consent from study participation) before documented progression or death	Date of last adequate tumor assessment	Censored
5	Documented progression	Date of documented progression. If a tumor assessment was done on multiple days, use the earliest date for that visit.	Progressed
6	Death without documented progression	Date of death	Progressed
7	Documented progression or death after missing 2 consecutive post-baseline tumor assessments	Date of last adequate tumor assessment before missed assessments or date of randomization, whichever is later	Censored

Note: Progression-free survival and associated outcome is determined by the earliest of the dates above, if more than 1 situation applies.

The PFS analysis is to test the superiority of LY2835219 to placebo in improving PFS time will use the log-rank test stratified by nature of disease (visceral metastases versus bone-only metastases versus other) and prior (neo)adjuvant endocrine therapy (aromatase inhibitor therapy versus other versus no prior endocrine therapy). The Kaplan-Meier method (Kaplan and Meier 1958) will be used to estimate the PFS curves as well as PFS rates at every 3 months for each treatment group. These rates will be compared based on a normal approximation for the difference between the rates.

The 3-look group-sequential design of the primary endpoint will be used to accommodate an event-driven plan for the interim and final analyses. There are 2 planned interim analyses and 1 final analysis for PFS in this study. The interim analyses are planned to take place after approximately 189 (approximately 70% of the planned) investigator-assessed PFS events have occurred and approximately 230 (approximately 85% of the planned) investigator-assessed PFS events have occurred. The cumulative 1-sided type I error rate of .025 will be maintained using the following method. At the first and second interim analysis, the nominal alpha levels will be

0.0001 and 0.00015, respectively. The remaining alpha will be spent at the final analysis. The resulting boundary p-value for the final analysis is dependent on the exact number of events observed at each analysis and can be calculated using the method of Slud and Wei (1982). If the 3 analyses are performed at exactly 189, 230, and 270 events, then the boundary p-value at the final analysis will be 0.0249994. The actual boundary for the final analysis will be calculated based on the actual number of events observed at the time of each analysis using software that implements the alpha-spending scheme noted above (for example, ADDPLAN 6.0, SAS 9.2, or similar software).

If statistical significance is not declared at the first interim PFS analysis, the second interim PFS analysis will be performed after 230 PFS events have been observed. Note that the second interim analysis of PFS will only be performed if statistical significance is not declared at the first interim PFS analysis. If statistical significance is not observed at either interim analysis, the final PFS analysis will be performed after approximately 270 PFS events have been observed based on investigator assessment.

Once statistical significance is declared at either interim analysis or the final analysis, the study will be positive based on the primary endpoint of PFS, and testing of secondary endpoints will proceed as described in the SAP.

The interim PFS analyses will be performed by DMC. The requirements for unblinding the sponsor at the interim analyses are found in Section 12.2.14.

The primary test of PFS will compare the 2 treatment groups using a log-rank test stratified by the randomization factors.

The Cox proportional hazard model (Cox 1972) with treatment as a factor will be used to estimate the hazard ratio and corresponding 95% CI with Wald's test p-value after stratifying for the same randomization variables specified for the primary analysis.

12.2.7. Secondary Outcomes and Methodology

The secondary objectives of the study are listed in Section 6.2.

12.2.7.1. Overall Survival

Overall survival is an important secondary endpoint for this study. To maintain the study-wise type I error rate, OS will be hierarchically tested; that is, OS will only be tested inferentially for significance only if the test of PFS is significant. Further details will be in the study SAP.

12.2.7.2. Objective Response Rate, Disease Control Rate, and Clinical Benefit Rate

The ORR, DCR, and CBR of each treatment arm will be calculated as defined by RECIST v1.1. All rates will be compared between treatment arms based on a normal approximation for the difference between the rates.

12.2.8. Sensitivity Analysis

Sensitivity analyses will be undertaken for calculation of the primary endpoint in order to evaluate the robustness of the analysis. The following sensitivity analyses will be performed for PFS:

Progression-Free Survival Sensitivity Analysis 1 (censoring for receiving subsequent systemic anticancer therapy): if a patient is initiated on another anticancer therapy prior to objective progression, including any postdiscontinuation treatment systemic therapy, radiotherapy, or surgical intervention, PFS will be censored at the date of the last complete objective progression-free disease assessment before initiation of the new therapy, regardless of whether or not this patient subsequently had objective progression or died.

Progression-Free Survival Sensitivity Analysis 2 (nonobjective progression as a PFS event): if a patient is discontinued from study treatment due to investigator determined non-objective progression (for example, symptomatic deterioration), then the patient's PFS time will be calculated using the date of non-objective progression as the progression date.

Progression-Free Survival Sensitivity Analysis 3 (forward-dating progressions at unscheduled assessments): if a patient has objective progression at an unscheduled disease assessment, then the PFS time for that patient will be forward-dated to the next scheduled disease assessment.

Progression-Free Survival Sensitivity Analysis 4. PFS will also be analyzed after adjusting for selected prognostic factors. Potentiall prognostic factors iincluded the stratification factors and other factors as outlined in the SAP. The hazard ratio for treatment effect will be estimated using a multivariate Cox proportional hazard model constructed by selecting variables among all the potential variables listed in the SAP, using stepwise selection method with entry p-value 0.05 and exit p-value 0.01. The treatment factor will be kept out of the model throughout the covariate selection process and only added into the final model.

Although this study is double-blinded, a blinded independent central review (BICR) of scans will be conducted on a randomly selected subset of patients to evaluate the potential for investigator bias in evaluation of time to progression, and hence the reliability of the treatment effect based on investigator assessment. Details concerning the size of the subset of patients, the analysis of this BICR data, and decision rules for conducting a central review of all patients will be described in a separate SAP.

An additional OS analysis will also be conducted based on the following definition using similar methods as stated in Section 12.2.7: time is defined as the time from the date of study enrollment to the date of death due to disease. Survival time will be censored on the date the patient was last known to be alive for patients who have no reported event. For patients that have died due to reasons not disease related, survival time will be censored at the date of death. Cause of death as reported by the investigator will be used in this analysis.

12.2.9. Pharmacokinetic and Pharmacodynamic Analyses

Pharmacokinetics analyses will be conducted on all patients who have received at least 1 dose of study treatment and have had samples collected (see PK sampling schedule in Attachment 7).

Mean population PK parameters for LY2835219 in plasma (clearance, exposure, volume of distribution, and half-lives) and inter-individual PK variability will be computed using nonlinear mixed-effect modeling implemented in NONMEM. Covariate effects (such as age, weight, sex, creatinine clearance, and plasma protein levels) on the PK parameters of LY2835219 in plasma will also be investigated.

Likewise, and if warranted by the data, mean population PK parameters for anastrozole or letrozole in plasma and inter-individual variability estimates will also be computed using nonlinear mixed-effect modeling implemented in NONMEM.

Finally, pharmacodynamic data (such as neutrophil, lymphocytes, or platelet counts in blood) collected in this study may be analyzed by means of NONMEM and connected to the population PK model for LY2835219 and/or NSAI in a PK/pharmacodynamic model.

12.2.10. Biomarker Analyses

The distributions of biomarkers with continuous measures, such a gene or protein expression, will be described. Summary statistics will include means, medians, corresponding standard errors, quartiles, and ranges. Biomarkers with discrete measures, such as genotype locus, will be summarized in frequency tables. Correlative analyses may be performed to investigate associations between biomarkers and clinical endpoints as deemed appropriate.

12.2.11. Health Outcome/Quality-of-Life Analyses

Patient-reported outcomes are measured through paper versions of the following:

- EORTC QLQ-C30 (The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30)
- EORTC QLQ-BR23 (The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Breast cancer)
- EQ 5D 5L (EuroQol 5-Dimension 5 Level)

For each patient with data from baseline and at least 1 post-baseline visit, the maximum change from baseline score will be calculated and summarized for EORTC scale scores. The reason and number of missing and incomplete questionnaires/assessments by visit will be summarized for each instrument and study arm.

Further analysis details will be described in the SAP.

12.2.11.1. Health-Related Quality of Life

EORTC QLQ-C30 instrument data will be scored as described by Aaronson and colleagues (Aaronson et al. 1993). If not already addressed in the EORTC scoring manual (Fayers et al.

2001), descriptive statistics for each EORTC QLQ-C30 item will be calculated. Descriptive statistics will be calculated for each dimension and the total score for each arm.

EORTC QLQ-BR23 data will be scored as described by the EORTC scoring manual (Fayers et al. 2001).

12.2.11.2. Resource Utilization

Utilization data will be summarized descriptively by category across arms (for example, analgesic use, bisphosphonate use, transfusions, radiation, surgery, and hospitalization days), including a frequency table with tabular statistics. Tests for differences in proportions between treatment groups and between response groups will be performed.

12.2.11.3. Health State Utility

The EQ-5D 5L data will be scored as described in an article by van Hout and colleagues (van Hout et al. 2012). The index score is calculated from a set of item weights to derive a score of 0 to 1, with 1 representing the best health status. Geographic-specific weights will be used as appropriate and when available. The VAS is scored from 0 (worst imaginable health state) through 100 (best imaginable health state) to represent the patient's self-report for each day. EQ-5D 5L responses for each item will be summarized by frequency and corresponding percentages. Descriptive statistics for the index and VAS will be calculated. Psychometric analyses, including calculation of reliability coefficients (Cronbach's alpha), will also be performed. The index scores and VAS will be analyzed using a repeated-measures model.

12.2.12. Safety Analyses

All safety summaries and analyses will be based upon the Safety Population as defined in Section 12.2.1.

Overall exposure to study drug, the numbers of patients completing each cycle, and the dose intensity will be summarized using descriptive statistics. The number of patients with any dose adjustment will be presented for entire treatment period as well as for each cycle. The number of patients with dose reductions, dose delays, or dose omissions will also be summarized, as will the reasons for dose adjustments.

AEs will be reported using the MedDRA dictionary. Investigators will report a verbatim AE term and a CTCAE v4.0 term and severity for all AEs. For analysis purposes, the following process will be used:

- The CTCAE v4 term reported by the investigator will be mapped to the MedDRA Preferred Term (PT) and System Organ Class (SOC) using the corresponding MedDRA Lower Level Term (LLT), unless the reported CTCAE term is 'Other - specify.'
- If the reported CTCAE term is 'Other - specify,' the MedDRA LLT, PT, and SOC centrally mapped from the verbatim AE term will be used.
- All listings and summaries will use the PT resulting from this process.

Preexisting conditions are defined as AEs that begin prior to the first dose of study drug.

A treatment-emergent adverse event (TEAE) is defined as an event that first occurred or worsened in severity after baseline. Comparisons of preexisting conditions to on-treatment events at the LLT level will be used in the treatment-emergent computation.

The following summaries will be produced by PT within SOC: preexisting conditions,, SAEs, TEAEs, drug-related TEAEs, and procedure-related TEAEs.

The following summaries will be produced by PT within SOC and maximum CTCAE grade: laboratory-based TEAEs, nonlaboratory-based TEAEs, drug-related laboratory-based TEAEs, and drug-related nonlaboratory-based TEAEs.

Reasons for death will be summarized separately for on-therapy and within 30 days of treatment discontinuation.

Hospitalizations and transfusions during the study treatment period or during the 30-day short-term follow-up period will be summarized by treatment group.

12.2.13. Subgroup Analyses

Subgroup analyses of PFS and OS will be performed for potential prognostic subgroup variables, including:

- All baseline stratification factors
- NSAI received while on study (letrozole versus anastrozole)
- Disease setting (de novo metastatic versus recurrent metastatic versus locoregionally recurrent)
- Measurable disease at baseline (yes versus no)
- Number of organs involved (1 versus 2 versus 3+)
- Age (<65 years versus 2'65 years)
- Region (North America, Europe, Asia, and Other)
- Race (Caucasian, Asian, and Other)
- PgR status (positive versus negative)
- Baseline ECOG PS (0 versus 1)

If a level of a factor consists of fewer than 5% of randomized patients, analysis within that level may be omitted. The final list of subgroup analyses will be provided in the SAP.

Analyses will be done within subgroup and, separately, across subgroups with a test of interactions of subgroups with treatment performed.

Other subgroup analyses may be performed as deemed appropriate.

12.2.14. Interim Analyses

12.2.14.1. Safety Interim Analyses

The DMC is responsible for providing external oversight of patient safety in Study JPBM independently of the Lilly study team and Lilly GPS.

During the study, safety interim analyses will be performed approximately every 3 months. The first safety interim analysis will be triggered by randomization of the 90th patient, with the data cutoff for this analysis occurring approximately 1 month after the trigger. The safety interim analyses will be conducted to evaluate the overall safety profile of LY2835219 when given in combination with NSAI. At the recommendation of the DMC, the frequency of safetty interim analyses may be modified.

At each interim analysis, the DMC may recommend the trial continue without modifications, continue with specific modifications, or be stopped for safety concerns. There will be no prespecified rules for stopping the trial due to safety concerns. The DMC me bers will review unblinded safety data at each interim analysis. If a significant safety signal is identified, the DMC may recommend a protocol amendment, termination of enrollmen , and/or termination of study treatment. The recommendations of the DMC will be communicated to the Lilly SMD and, if necessary, an IRC.

In the event that safety monitoring uncovers an issue that n eds to be addressed by unblinding at the treatment group level, members of the DMC can conduct additional analyses of the safety data. Additionally, unblinding of a limited number of Lilly representatives external to the study team may be required for evaluation of selected SAEs for determination of regulatory reporting.

12.2.14.2. Efficacy Interim Analyses

Two efficacy interim analyses of PFS are planned, as described in Section 12.2.6. Four interim analyses of OS are planned (at the time of each of the 2 interim PFS analyses, at the time of the final PFS analysis, and at the time when approximately 75% of the OS events have been observed; subsequently, a final OS analysis is planned).

The interim PFS analyses will be conducted to provide early efficacy information and could potentially result in early communication with regulatory agencies. This analysis will be performed by an independent Statistical Analysis Group and provided to the DMC. The DMC should recommend unblinding the sponsor if the following are observed:

- The analysis of investigator-assessed PFS is significant at the alpha level specified in Section 12.2.6 with the observed stratified hazard ratio for investigator-assessed PFS less than 0.56 at the first interim analysis, or is less than 0.6 at the second interim analysis, and
- Results of the analysis of the centrally reviewed PFS support the results of the investigator-assessed PFS analysis.

If the analysis of PFS is positive based on these requirements, the DMC will be instructed to recommend to the SMD that the sponsor be unblinded. The SMD may convene an IRC to review the DMC's recommendation prior to sponsor unblinding.

Overall survival will be analyzed as described in Section 12.2.7. Results of OS analyses will not be communicated until a significant result is observed or the final PFS analysis is performed

The sponsor has no intent to stop the study based on interim analysis of efficacy, and all patients will continue follow-up for PFS until the primary PFS analysis and for OS until study close. Patients randomized to the control group will not be permitted to cross over to the experimental group, as this will confound the assessment of OS. In addition, patients willl remain blinded for the duration of the study unless the criteria in Section 9.5 are met. If the DMC makes a recommendation counter to this, for example, the DMC recommends crossing all patients over to the experimental treatment, FDA will be consulted before any action is taken as well as other regulatory agencies if deemed appropriate.

The unblinded review of the analyses, including review of the efficacy along with the safety data, will be conducted by DMC. Study sites will receive information about interim results ONLY if they need to know for the safety of their patients.

Unblinding details are specified in the unblinding plan section of the SAP.

12.2.14.3. Pharmacokinetic/Pharmacodynamic Interim Analyses

A limited number of preidentified individuals independent of the study team may receive access to unblinded data, as specified in the unblinding plan, prior to the interim or final database lock, in order to initiate the final population PK/pharmacodynamic model development processes for interim or final analyses. Information that may unblind the study during the analyses will not be reported to study sites or blinded study team until the study has been unblinded.

13. 1nformed Consent, Ethical Review, and Regulatory Considerations

13.1. 1nformed Consent

The investigator is responsible for ensuring that the patient understands the potential riskss and benefits of participating in the study, including answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the trial.

The ICF will be used to explain the potential risks and benefits of study parttiicipation to the patient in simple terms before the patient is entered into the study, and to document that the patient is satisfied with his or her understanding of the risks and beneffittss of participating iin the study and desires to participate in the study.

The investigator is responsible for ensuring that informed consent is given by each patient. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of study drug.

As used in this protocol, the term "informed consent" includes all consent given by patients.

13.2. Ethical Review

Lilly or its representatives must approve all ICFs before they are used at the investigative site[s]. All ICFs must be compliant with the International Conference on Harmonisation (ICH) guideline on GCP.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site[s].

The study site's ERB[ss]] should be provided with the following:

- the current IB or package labeling and updates during the course of the study
- ICF
- relevant curricula vitae

13.3. Regulatory Considerations

This study will be conducted in accordance with:

- consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- the ICH GCP Guideline (E6)
- applicable laws and regulations.

The investigator or designee will promptly submit the protocol to applicable ERB(s).

Some of the obligations of Lilly will be assigned to a third-party organization.

An identification code assigned by the investigator to each patient will be used in lieu of the patient's name to protect the patient's identity when reporting AEs and/or other trial-related data.

13.3.1. Investigator Information

Site-specific contact information may be provided in a separate document.

Physicians with a specialty in oncology will participate as investigators in this clinical trial.

13.3.2. Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

13.3.3. Final Report Signature

The clinical study report (CSR) coordinating investigator will sign the final CSR for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

Lilly will select an investigator to serve as the CSR coordinating investigator.

The Lilly responsible medical officer and statistician will sign/approve the final clinical study report for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

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Attachment 1. Protocol JPBM Study Schedule

Protocol I3Y-MC-JPBM

Baseline Schedule		Study Period	Baseline (BL)		
		Visit	0		
		Approximate Visit Duration (days)	Up to 28		
		Relative day to C1D1	≤28	≤14	
Procedure Category	**Procedure**	**Protocol Reference**			**Comments**
Study Entry /Enrollment	Informed Consent Form signed	**Section 13.1**	X		Prior to conducting any protocol-specific tests / procedures
	Inclusion/Exclusion evaluation	**Section 7**		X	
Medical History	Initial medical history/preexisting conditions			X	
	Historical illnesses			X	Include habits assessment of alcohol and tobacco use
Physical Examination	Physical examination			X	Include but not limited to height and weight
	Vital Signs			X	Include blood pressure, pulse, respiratory rate, and temperature
	ECOG performance status	**Attachment 4**		X	
Tumor Assessment	Tumor measurement (palpable or visible)	**Section 10.1.1**	X		Photography of skin lesions with ruler required, if applicable
	Radiologic imaging according to RECIST 1..1	**Section 10.1.1** **Attachment 5**	X		Performed locally. For patients with locoregionally recurrent breast cancer, MRI scan of the breast; additionally, for all patients, CT or MRI scan of the chest, abdomen, and pelvis. CT scan is the best currently available and reproducible method to measure lesions selected for response assessment; it is recommended that CT imaging of the abdomen and pelvis be performed with IV contrast whenever possible. MRI may be used instead of CT in selected instances. Gadolinium-enhanced MRI is preferred if hypersensitivity to contrast.
	Bone Scintigraphy	**Section 10.1.1** **Attachment 5**	X		Performed locally. Bone scintigraphy performed as part of routine clinical care within 45 days before Cycle 1 Day 1 is also acceptable.
	X-ray, or CT scan with bone windows, or MRI	**Section 10.1.1** **Attachment 5**	X		Performed locally. *For on/y those patients with bone /esions identified by bone scintigraphy at base/ine,* all bone lesions will be evaluated at baseline by focused studies to enable serial assessment.

Protocol I3Y-MC-JPBM

Baseline Schedule

		Study Period	Baseline (BL)		
		Visit	0		
		Approximate Visit Duration (days)	Up to 28		
		Relative day to C1D1	≤28	≤14	
Procedure Category	**Procedure**	**Protocol Reference**			**Comments**
Adverse Event Collection/CTCAE Grading		**Section 10.3**	X		CTCAE = Common Terminology Criteria for Adverse Events
Concomitant Medication Notation		**Section 9.6**	X		Note: RANK-L or bisphosphonate agents should be initiated 2'7 days prior to randomization, if applicable.
Lab/ Diagnostic Tests	Central hematology	**Attachment 2**		X	Enrollment and treatment decisions may be based upon results of tests performed locally. If local laboratory tests a e used for this purpose, then a duplicate specimen must be submitted to the central laboratory. Discrepancies between local and central laboratory that may have an impact on eligibility or treatment decisions will not be con idered protocol deviations
	Central chemistry	**Attachment 2**		X	Enrollment and treatment decisions may be based upon results of tests performed locally. If local laboratory tests are used for this purpose, then a duplicate specimen must be submitted to the central laboratory. Discrepancies between local and central laboratory that may have an impact on eligibility or treatment decisions will not be considered protocol deviations.
	Local FSH and estradiol level	**Attachment 2**		X	Required only for women < 60 years with amenorrhea for at least 12 months to confirm post-menopausal status
	Local ECG	**Section 10.3.2.1**		X	Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

Abbreviations: CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FSH = follicle stimulating hormone; IV = intravenous; MRI = magnetic resonance imaging; RANK-L = RANK ligand; RECIST = Response Evaluation Criteria in Solid Tumors.

Protocol 13Y-MC-JPBM

During Treatment Study Schedule

Procedure Category	Procedure	Protocol Reference	Study Treatment Period						Comments
		Cycle / Visit	1	2		3	4-X		
		Approximate Visit Duration (days)	28	28		28	28		
		Relative day within a cycle	1	1	21-28	1	1	21-28	
Physical Examination	Physical Exam		X	X		X	X		Include but not limited to weight
	Vital Signs		X	X		X	X		e blood pressure, pulse, respiratory rate, and temperature.
	ECOG performance status	Attachment 4	X	X		X	X		
Archived Tumor Tissue		Section 10.4.2.1	X						Whole or partial block or 15 - 20 slides should be provided upon patient randomization.
Adverse Event Collection/CTCAE Grading		Section 10.3	X	X		X	X		
Concomitant Medication Notation		Section 9.6	X	X		X	X		
Lab/ Diagnostic Tests	Central hematology	Attachment 2	X	X		X	X		Central hematology labs may be drawn up to 3 days prior to Day 1 of each cycle. Additional local hematology labs may be drawn for treatment adjustment and patient management purposes.
	Central chemistry	Attachment 2	X	X		X	X		Central chemistry labs may be drawn up to 3 days prior to Day 1 of each cycle. Additional local chemistry labs may be drawn for treatment adjustment and patient management purposes.
	Pharmacokinetic (PK) sampling	Attachment 7	X	X		X			See Attachment 7 for specific timing.
	Pharmacogenetic blood sample	Section 10.4.2.2	X						Draw sample before patient is dosed on C1D1.
	Biomarker plasma sample	Section 10.4.2	X	X					Draw sample before patient is dosed on C1D1 and upon arrival at site on C2D1.
	Local ECG	Section 10.3.2.1	X	X			X		2 to 4 hours after the LY dose on Cycle 1 Day 1, upon arrival at site on Cycle 2 Day 1, 2 to 4 hours after the LY dose on Cycle 4 Day 1. Following C4D1, no additional ECGs are required while the patient is on treatment (only subsequently for short-term follow-up). Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

Protocol I3Y-MC-JPBM

During Treatment Study Schedule

		Study Treatment Period						
	Cycle / Visit	**1**	**2**		**3**	**4-X**		
	Approximate Visit Duration (days)	28	28		28	28		
	Relative day within a cycle	1	1	21-28	1	1	21-28	
Procedure Category	**Procedure**	**Protocol Reference**						**Comments**
Tumor Assessment	Tumor measurement (palpable or visible)	**Section 10.1.1**			X	X		Skin lesions identified at baseline require repeat photographic images on Day 1of every second cycle beginning with Cycle 3 and continuing through Cycle 19 (inclusive), on Day 1of every third cycle after Cycle 19, and within 14 days of clinical progression. Photographic images may be taken more frequently based upon the discretion of the investigator or following the identification of new skin lesions post-baseline.
	Radiological imaging according to RECIST (CT scan/MRI)	**Section 10.1.1 Attachment 5**		X			X	Performed locally. For patients with locoregionally recurrent breast cancer not amenable to curative treatment, MRI scan of the breast is performed, if applicable, in addition to other scans. Imaging studies (Breast MRI and CT scan or MRI of the chest, abdomen, and pelvis) will be repeated on Day 21 to Day 28 of every second cycle beginning with Cycle 2 and continuing through Cycle 18 (inclusive), on Day 21 to Day 28 of every third cycle after Cycle 18, and within 14 days of clinical progression. The same method of imaging used at baseline should be used for each subsequent assessment.
	Bone Scintigraphy	**Section 10.1.1 Attachment 5**					X	Performed locally. Repeat for all patients on Day 21 to Day 28 of every sixth cycle beginning with Cycle 6. In addition, bone scans should be repeated even if a complete response is identified in target disease or progression in bone is suspected. Importantly, RECIST v1.1 emphasizes that bone scintigraphy is not adequate to measure bone lesions; however, bone scintigraphy can be used to confirm the presence or disappearance of bone lesions.
	X-ray, CT scan with bone windows, or MRI	**Section 10.1.1 Attachment 5**		X			X	Performed locally for patients with bone lesions identified by bone scintigraphy at baseline. Repeat on Day 21 to Day 28 of every second cycle beginning with Cycle 2 and continuing through Cycle 18 (inclusive), on Day 21 to Day 28 of every third cycle after Cycle 18, and within 14 days of clinical progression. For patients with new lesions identified by post-baseline bone scintigraphy, targeted assessment by X-ray, CT scan with bone windows, or MRI will be performed to confirm findings.

Protocol I3Y-MC-JPBM

During Treatment Study Schedule

			Study Treatment Period						
		Cycle / Visit	**1**	**2**		**3**	**4-X**		
		Approximate Visit Duration (days)	28	28		28	28		
		Relative day within a cycle	1	1	21-28	1	1	21-28	
Procedure Category	**Procedure**	**Protocol Reference**							**Comments**
Health Outcomes	EORTC QLQ-C30, EORTC QLQ-BR23, EQ-5D 5L	**Section 10.2**	X			X	X		Patients complete prior to extensive interaction with site staff. On Cycle 1 Day 1, questionnaires must be administered prior to the first dose of study tre tment. Questionnaires should be administered on Cycle1 Day 1, and then Day 1 of every second cycle beginning with Cycle 3 through Cycle 19, and on Day 1of every third cycle after Cycle 19.
Study Drug	LY2835219 or Placebo (blinded randomization)	**Section 9.1**	Take 150 mg or prescribed dose orally every 12 hours on Days 1 through 28 of every cycle, with the exception that the second dose on C1D1 should be omitted to allow for adequate study drug for at home dosing on C2D1.						On Cycle 1 Day 1 only, patients should take one single dose of blinded study drug and initiate chronic every 12 hour dosing on Cycle 1 Day 2. On Cycle 2 Day 1, patients will take medication at home at least 4 hours prior to arrival at the clinic. On Cycle 4 Day 1, patients will take morning dose of blinded study drug in the clinic.
Co-Administered Drug (per investigator selection)	anastrozole	**Section 9.1**	Take 1mg tablet orally every 24 hours on Days 1 through 28						For PK and ECG purposes, should be taken at the same time as, or up to 20 minutes after the morning dose of blinded study drug. Adjustment to timing of dose administration may be made at the discretion of the investigator after Cycle 4 Day 1.
	letrozole	**Section 9.1**	Take 2.5mg tablet orally every 24 hours on Days 1 through 28						For PK and ECG purposes, should be taken at the same time as, or up to 20 minutes after the morning dose of blinded study drug. Adjustment to timing of dose administration may be made at the discretion of the investigator after Cycle 4 Day 1.

Abbreviations: C4D1 = Cycle 4 Day 1; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-BR23 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Breast cancer; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D 5L = EuroQol 5-Dimension 5 Level; MRI = magnetic resonance imaging; RECIST = Response Evaluation Criteria in Solid Tumors.

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Post Treatment Discontinuation Study Schedule

		Study Period	**Post-Discontinuation Short Term Follow-Up**	**Postdiscontinuation Long Term Follow-Up**	
		Visit	**801**	**802-X**	
		Approximate Visit Duration (days)	**30±5**	**Variable**	
		Relative day	**30**		
Procedure Category	**Procedure**	**Protocol Reference**			**Comments**
Physical Examination	Physical Exam		X		Includes but not limited to weight
	Vitals		X		Includes blood pressure, pulse, respiratory rate, and temperature.
	ECOG Performance Status	**Attachment 4**	X		
Tumor Assessment	Tumor measurement (palpable or visible)	**Section 10.1.1**	X	X	**ONLY For patients who discontinue study treatment without objectively measured progressive disease (PD),** continue to conduct tumor assessments approximately every 8 weeks for the first 18 months following randomization and thereafter approximately every 12 weeks until the patient has objective disease progression or until study completion. After the patient has objective disease progression, photographic images are no longer required and the patient will continue with post-discontinuation follow-up approximately every 12 weeks until the patient's death or overall study completion.
	Bone Scintigraphy	**Section 10.1.1** **Attachment 5**	X	X	**ONLY For patients who discontinue study treatment without objectively measured progressive disease (PD),** continue to evaluate repeat bone scans approximately every 6 months until objective disease progression or study completion.
	Radiologic imaging according to RECIST	**Section 10.1.1** **Attachment 5**	X	X	The same method of imaging used at baseline should be used for each subsequent assessment. **ONLY For patients who discontinue study treatment without objectively measured progressive disease (PD)**, continue to conduct tumor assessment approximately every 8 weeks for the first 18 months following randomization and thereafter approximately every 12 weeks by the same method used at baseline and throughout the study until the patient has objective disease progression or until study completion. After the patient has objective disease progression, radiologic tests are no longer required and the patient will continue with post-discontinuation follow-up approximately every 12 weeks until the patient's death or overall study completion

Protocol I3Y-MC-JPBM

Post Treatment Discontinuation Study Schedule

		Study Period	Post-Discontinuation Short Term Follow-Up	Postdiscontinuation Long Term Follow-Up	
		Visit	801	802-X	
		Approximate Visit Duration (days)	30±5	Variable	
		Relative day	30		
Procedure Category	**Procedure**	**Protocol Reference**			**Comments**
Tumor Assessment continued	X-ray, CT scan with bone windows, or MRI	**Section 10.1.1 Attachment 5**	X	X	**ONLY For patients who discontinue study treatment without objectively measured progressive disease (PD), focused studies are** performed for patients with bone lesions previously identified by bone scintigraphy. During long term follow up period, repeat scans should performed approximately every 8 weeks for the first 18 months following randomization, and subsequently approximately every 12 weeks until disease progression or tudy completion.
Survival Information		**Section 10.1.4**	X	X	Although preferable to collect during a clinic visit, survival information may be collected by contacting the patient or family directly (for example, via telephone) if no procedures required. This should be collected at minimum every 90 days if no other procedures are performed. Additional long-term follow-up data collection will include post-discontinuation anticancer therapies.
Adverse Events Collection/CTCAE Grading		**Section 10.3**	X	X	After Visit 801, only study protocol or drug-related events are reported. If a patient has ongoing AE or SAE possibly related to study drug (not co-administered drug) (for instance, abnormal electrolytes), the patient should be followed until the event is resolved, the event is no longer considered to be drug-related, the event becomes stable or returns to baseline, a new treatment is initiated for the patient, or the patient dies or is lost to follow-up. Any subsequent follow-up(s) for AEs will be no more than 30 days ± 5 days in duration.
Concomitant Medications Notation		**Section 9.6**	X		
Lab/ Diagnostic Tests	Central hematology	**Attachment 2**	X		
	Central chemistry	**Attachment 2**	X		
	Biomarker plasma sample	**Section 10.4.2**	X		Draw sample only for patients discontinuing due to PD.
	ECG	**Section 10.3.2.1**	X		Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.
Health Outcomes	EORTC QLQ-C30, EORTC QLQ-BR23, EQ-5D 5L	**Section 10.2**	X		

Protocol I3Y-MC-JPBM
Post Treatment Discontinuation Study Schedule

Abbreviations: AE = adverse event; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-BR23 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Breast cancer; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D 5L = EuroQol 5-Dimension 5 Level; MRI = magnetic resonance imaging; PK = pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumors; SAEs = serious adverse events.

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Study Schedule for the Continued Access Period only

	Study Period	Patients on Study Treatment	Continued Access Period Follow-Up	
	Cycle	X	Follow-Up[a]	
	Visit	501-5XX	901	
	Approximate Visit Duration (days)	28±3	30±5	
	Relative day within a cycle	1		
Procedure Category / **Procedure**	**Protocol Reference**			**Comments**
Adverse Events Collection/CTCAE Grading	**Section 10.3**	X	X	Data on SAEs that occur before the end of trial will be stored in the collection database and the Lilly safety system
Study Drug / LY2835219	**Section 9.1**	X		Only patients assigned to LY2835219 at randomization and receiving clinical benefit will continue to receive LY2835219 during the continued access period. LY2835219 is to be administered orally every 12 hours on Days 1 through 28 of each cycle. Patients who were assigned to placebo, will no longer receive placebo during the continued access period and cannot crossover to LY2835219.
Co-Administered Drugs / Anastrozole	**Section 9.1**	X		Patients receiving clinical benefit will continue to receive anastrozole or letrozole during the continued access period. Anastrozole or letrozole is to be administered orally every 24 hours on Days 1 through 28 of each cycle
Co-Administered Drugs / Letrozole	**Section 9.1**	X		

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; OS = overall survival; SAEs = serious adverse events.

[a] The continued access period begins after study completion (that is, after final OS analysis) and ends at the end of trial (that is, the last patient visit).

Attachment 2. Protocol JPBM Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology[a]:	**Clinical Chemistry**[a,d]:
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
Mean cell volume (MCV)	Total Protein
Mean cell hemoglobin concentration (MCHC)	Total bilirubin
Leukocytes (WBC)	Direct bilirubin
Neutrophils, (segmented and bands)	Alkaline phosphatase
Lymphocytes	Alanine aminotransferase (ALT)
Monocytes	Aspartate aminotransferase (AST)
Eosinophils	Blood urea nitrogen (BUN)
Basophils	Creatinine
Platelets	Calcium
	Albumin
	Follicle Stimulating Hormone (FSH) level[b,c]
	Estradiol level[b,c]

Abbreviations: RBC = red blood cells; WBC = white blood cells.

a Assayed by Lilly-designated (central) laboratory.

b Local or investigator-designated laboratory.

c To be performed at baseline in order to establish eligibility only for women <60 years and ammenorrheic for at least 12 months.

d Per the lletrozole and anastrozole labels, investigators should consider monitoring cholesterol. The decision to monitor and frequency of monitoring are at the discretion of the investigator.

Attachment 3. Protocol JPBM Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow up with patients in consultation with the Lilly clinical research physician.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin Time
WBC	Prothrombin Time, INR
Neutrophils, segmented and bands	
Lymphocytes	**Hepatic Serology[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-nuclear antibody[a]**
AST	
GGT	**Anti-smooth muscle antibody[a]**
CPK	

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; GGT = gamma glutamyl transferase; Ig = immunoglobulin; INR = international normalized ratio; RBC = red blood cells; WBC = white blood cells.

a Assayed by Lilly-designated laboratory.

b Reflex/confirmation dependent on regulatory requirements and/or testing availability.

Attachment 4. Protocol JPBM ECOG Performance Status

ECOG Performance Status

Activity Status	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work offa light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of alllll selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead.

Abbreviation: ECOG = Eastern Cooperative Oncology Group. Source: Oken et al. 1982.

Attachment 5. Protocol JPBM REC1ST Criteria 1.1

Response and progression will be evaluated in this study using the international criteria proposed by the New Response Evaluation Criteria in Solid Tumors (RECIST): Revised RECIST Guideline (version 1.1; Eisenhauer et al. 2009).

Measurability of Tumor at Baseline

Tumor lesions/lymph nodes will be categorized at baseline as measurable or nonmeasurable. Measurable disease is defined by the presence of at least 1 measurable lesion.

Measurable

Tumor lesions: Measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (slice thickness ≤5 mm)
- 10 mm caliper measurement by clinical exam (non-measurable lesions if cannot be accurately measured with calipers)
- 20 mm by chest x-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan thickness recommended to be ≤5 mm).

Nonmeasurable

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly nonmeasurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitis involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measureable by reproducible imaging techniques.

Special Considerations for Lesion Measurability

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI, can be considered measurable lesions if the soft tissue component meets the definition of measurability.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable)
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability. If noncystic lesions are presented in the same patients, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

- Tumor lesions situated at a previously irradiated area, or in an area subjected to other loco-regional therapy, are non-measurable unless there has been demonstrated progression in the lesion.

Baseline Documentation of Target and Non-Target Lesion

Target Lesions

When more than 1 measurable lesion is present at baseline, all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Non-nodal Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and can be reproduced in repeated measurements.. Measurable lymph nodes are target lesions if they meet the c iteria of a short axis of ≥15 mm by CT scan. All measurements are to be recorded in the case record form (CRF) in millimeters (or decimal fractions of centimeters [cm]).

Nontarget Lesions

All other lesions (or sites of disease) are identiified as nontarget lesions (chosen based on their representativeness of involved organs and the ability to be reproduced in repeated measurements) and should be recorded at baseline. Measurement of these lesions are not required but should be followed as 'present,' 'absent,' or in rare cases 'unequivocal progression.' In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the CRF (for example, multiple liver metastases recorded as 1 liver lesion).

Lymph nodes with short axis ≥10 mm but <15 mm should be considered nontarget lesions. Nodes that have a short axis <10 mm are considered nonpathological and are not recorded or followed.

Specifications by Methods of Measurement

All measurements should be recorded in metric notation, using a ruler or calipers if clinically assesse . All baseline evaluations should be performed as closely as possible to the beginning of treat ent and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is

should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessed by clinical exam.

An adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient. If prior to enrollment it is known a patient is not able to undergo CT scans with IV contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (with or without IV contrast) should be used to evaluate the patient at baseline and follow-up should be guided by the tumor type under investigation and the anatomic location of the disease.

C/inica/ Lesions: Clinical lesions will only be considered measurable when they are superficial and ≥10 mm diameter as assessed using calipers (for example, skin nodules). For the case of skin lesions, documentation by color photography, including a rulerr to estimate the size of the lesion is recommended. When lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may be reviewed at the end of the study.

Chest X-Ray: Chest CT is preferred over chest x-ray when progression is an important endpoint. Lesions on chest x-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT and MRI: CT scan is the best currently available and reproducible method to measure lesions selected for response assessment. Measurability of lesions on CT scan is based on the assumption that CT slice thickness iss≤5 mm. When CT scan have slice thickness >5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (for example, for body scans). If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

U/trasound: Ultrasound should not be used to measure lesion size. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor Markers: Tumor markers alone cannot be used to assess tumor response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete response (CR). Specific guidelines for both prostate-specific antigen (PSA) response ((in recurrent prostate cancer) and CA-125 response (in recurrent ovarian cancer) have been published.

Cyto/ogy, Histo/ogy: These techniques can be used to differentiate between partial responses (PR) and complete response (CR) in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (for example, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease (SD) in order to differentiate between response (or SD) and progressive disease (PD).

Pet Scan (FDG-PET, PET CT): PET is not recommended for lesion assessment. If a new lesion is found by PET, another assessment must be done by CT, unless the PET CT is of diagnostic quality. If CT is done to confirm the results of the earlier PET scan, the date of progression must be reported as the earlier date of the PET scan.

Bone Scan: If lesions measured by bone scan are reported at baseline, it is necessary to repeat the bone scan when trying to identify a complete response (CR) or partial response (PR) in target disease or when progression in bone is suspected.

Response Criteria

Evaluation of Target Lesions

Comp/ete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. Tumor marker results must have normalized.

Partia/ Response (PR): At least a 30% decrease in the sum of diameter of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (including the baseline sum if that is the smallest). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of 1 or more new lesions is also considered progression.

For equivocal findings of progression (for example, very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Stab/e Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Not Eva/uab/e: When an incomplete radiologic assessment of target lesions is performed or there is a change in the method of measurement from baseline that impacts the ability to make a reliable evaluation of response.

Evaluation of Nontarget Lesions

Comp/ete Response: Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be non-pathological or normal in size (<10mm short axis).

Non-CR/ non-PD: Persistence of 1 or more nontarget lesions and/or maintenance of tumor marker level above the normal limits.

Progressive Disease: Unequivocal progression of existing nontarget lesions. The appearance of 1 or more new lesions is also considered progression.

Not Eva/uab/e: When a change in method of measurement from baseline occurs and impacts the ability to make a reliable evaluation of response.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the earliest of objective progression or start of new anticancer therapy, taking into account any requirement for confirmation. The patient's best overall response assignment will depend on the findings of both target and nontarget disease and will also take into consideration the appearance of new lesions. The Best Overall Response will be calculated via an algorithm using the assessment responses provided by the investigator over the course of the trial.

Time Point Response

It is assumed that at each protocol-specified time point, a response assessment occurs. (When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point.) Table 1 provides a summary of the overall response status calculation at each time point for patients who have *measurab/e disease* at baseline.

Table 1. Time Point Response: Patients with Target (± Nontarget) Disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not allll evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR = complete response; PR = partial response; SD = stable disease.; PD = progressive disease; NE = inevaluable.

Table 2 is to be used when patients have *nonmeasurab/e* disease only.

Table 2. Time Point Response: Patients with Nontarget Disease Only

Nontarget Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Abbreviations: CR = complete response; PD = progressive disease ; NE = inevaluable.

[a] non-CR/non-PD is preferred over SD for nontarget disease.

Frequency of Tumor Re-Evaluation

A baseline tumor evaluation must be performed within 4 weeks before patie t begins study treatment. Frequency of tumor re-evaluation while on and adapted to tre tment should be protocol-specific and adapted to the type and schedule of treatment. I the context of Phase 2 studies where the beneficial effect therapy is not known, follow-up every 6-8 weeks is reasonable. Normally, all target and non-target sites are evaluated at each assessment using the same method. However, bone scans may need to be repeated only when CR is identified in target disease or when progression in bone is suspected.

Confirmatory Measurement/Duration of Response

Confirmation:
The main goal of confirmation of objective response in clinical trials is to avoid overestimating the response rate observed. The confirmation of response is particularly important in *nonrandomized tria/s* where response (CR/PR) is the primary end point. In this setting, to be assigned a status of PR/CR, changes in tumor measurements must be confirmed by repeat assessmentss that should be performed no less than 4 weeks after the criteria for response are first met. To confirm a response of CR, a full assessment of all target and nontarget lesions that were present at baseline must occur, including those measured by bone scan. To confirm a PR or SD, a full assessment of target lesions that were present at baseline must occur; assessment of nontargets is not required.

However, in *randomized tria/* (Phase 2 or 3) or studies where SD or progression is the primary endpoints, confirmation of response is not required. But, elimination of the requirement may increase the importance of central review to protect against bias, in particular of studies which are not blinded.

IIn the case of SD, follow-up measurements must have met the SD criteria at least once after start of treatment at a minimum interval not less than 6 weeks measured from randomization.

Duration of Overa// Response
The duration of overall response is measured from the time measurement criteria are first met for CR or PR (whichever is first recorded) until the first date that disease is recurrent or objective progression is observed (taking as reference for PD the smallest measurements recorded on study).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of Stab/e Disease
Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for objective progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, that is the reference for calculation of PD).

1ndependent Review of Response and Progression

When objective response (CR + PR) is the primary end point, and when key drug development decisions are based on the observation of a minimum number of responders, it is recommended that all claimed responses be reviewed by an expert(ss) independent of the study. If the study is a randomized trial, ideally reviewers should be blinded to treatment assignment.

Attachment 6. Protocol JPBM Sampling Summary

This table summarizes the purpose for sampling, sample types, maximum volume per sample, maximum number of samples, and maximum total volume during the study. The summary below provides estimates. More samples could be required in the case of retests, additional health monitoring (if needed), or for patients continuing treatment beyond the protocol-specified number of cycles in the study. Fewer samples may actually be taken (for example, patients who discontinue from the study).

Protocol I3Y-MC-JPBM Sampling Summary[a]

Purpose	Sample Type	Maximum Amount per Sample	Maximum Number Samples	Maximum Total A ount
Screening/Study qualification (Hematology and Clinical Chemistry)	Blood	7 mL	1	7 mL
Safety/Health monitoring (Hematology and Clinical Chemistry)	Blood	7 mL	17	119 mL
Pharmacokinetic sample	Blood	4 mL	5	20 mL
Pharmacogenetic blood sample	Blood	10 mL	1	10 mL
Biomarker plasma sample	Blood	6 mL	3	18 mL
Total blood volume	Blo d			174 mL
Hepatic monitoring[b]	Blood	3 - 30 mL	-	-

a Covers Cycles 1 through 16 and one post-discontinuation follow up visit.

b Based on laboratory safety values, unscheduled hepatic monitoring testing may be performed as part of patient follow-up, in consultation with the designated medical monitor.

Attachment 7. Protocol JPBM Electrocardiogram and Pharmacokinetic Sampling Schedule

The schedule for PK sampling is summarized in the table below. The date and exact time of collection for each venous blood sample should be documented on the laboratory requisition.

Pharmacokinetic Sampling Schedule

Cycle(C) and Day(D)	ECG	PK Sample Number	Study Drug Dose	Dosing of anastrozole / letrozole	Sampling Time for ECG and PK from Blood[a]
Baseline (Day -14 to Day -1)	X				Day of visit
C1D1	X	1	X[b]	X[b]	2-4hrs after NSAI and blinded study drug dosed in clinic
C2D1	X	2	X[c]	X[c]	Upon arrival at site (that is, at least 4 hrs after taking NSAI and blinded study drug doses at home)
C2D1		3			3±0.5 hrs after arrival at site (that is, at least 7±0.5 hrs after taking NSAI and blinded study drug doses at home.
C3D1		4	X[b]	X[b]	Prior to NSAI and blinded study drug doses. Patient is dosed in clinic after sample collection.
C3D1		5			3±0.5hrs after NSAI and blinded study drug dosing in clinic
C4D1	X		X[b]	X[b]	2-4hrs after NSAI and blinded study drug dosing in clinic.
30 Day Follow-Up	X				Day of visit

Abbreviation: hrs = hours; NSAI = nonsteroidal aromatase inhibitor; PK = pharmacokinetic.

[a] Samples of approximately 4 mL of whole blood will be drawn from at least 150 patients randomized in the study for measurement of study treatment and LY2835219 metabolites concentrations.

[b] Patient is administered NSAI and study drug doses in clinic. On Cycle 1 Day 1 only, patients should take one single dose of blinded study drug and initiate chronic every 12 hours dosing on Cycle 1 Day 2

[c] Patient should take NSAI and study drug doses at home at least 4 hours before arrival at site. The time of NSAI and study drug dose intake must be recorded that day..

Attachment 8. Protocol JPBM 1nducers, Strong 1nhibitors of CYP3A, or Substrates of CYPs with Narrow Therapeutic Range

The information in this attachment is provided for guidance to investigators and does not preclude the use of these medications if clinically indicated.

Inducers of CYP3A
Carbamazepine
Dexamethasone[a]
Phenobarbital/phenobarbitone
Phenytoin
Rifapentine
Rifampin
Rifabutin
St. John's wort

[a] Important note: All patients may receive supportive therapy with dexamethasone, prefera ly ≤7 days, if clinically indicated.

Strong inhibitors of CYP3A
All HIV protease inhibitors
Clarithromycin
Itraconazole
Ketoconazole
Nefazodone

Cytochrome P450 Substrates with Narrow Therapeutic R nge

Cytochrome P450	**Substrate**
CYP1A2	Theophylline
	Tizanidine
CYP2C8	Paclitaxel
CYP2C9	Warfarin
	Phenytoin
CYP2D6	Thioridazine
	Pimozide
CYP3A	Alfentanil
	Astemizole
	Cisapride
	Cyclosporine
	Dihydroergotamine
	Ergotamine
	Fentanyl
	Pimozide
	Quinidine
	Sirolimus
	Tacrolimus
	Terfenidine

Attachment 9. Protocol JPBM CTCAE 4.03 Diarrhea Definition

Diarrhea will be evaluated in this study using the criteria proposed by Common Terminology Criteria for Adverse Events (CTCAE) v4.0 revised: CTCAE 4.03-June 14, 2010: Gastrointestinal disorders.

Gastrointestinal Disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline.	Increase of 4-6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase > 7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: a disorder characterized by frequent and watery bowel movements					

Abbreviation: ADL = Activities of Daily Living.

Attachment 10. Protocol JPBM Amendment (a) Summary A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Nonsteroidal Aromatase 1nhibitors (Anastrozole or Letrozole) plus LY2835219, a CDK4/6 1nhibitor, or Placebo in Postmenopausal Women with Hormone Receptor-Positive, HER2-Negative Locoregionally Recurrent or Metastatic Breast Cancer with No Prior Systemic Therapy in this Disease Setting

Study I3Y-MC-JPBM A Randomized, Double-Blind, Placebo-Controlled, Phase 3 St dy of Nonsteroidal Aromatase Inhibitors (Anastrozole or Letrozole)) plus LY2835219, a CDK4/6 Inhibitor, or Placebo in Postmenopausal Women with Hormone Receptor-Posittive, HER2-Negative Locoregionally Recurrent or Metastatic Breast Cancer with No Prior Systemic Therapy in this Disease Setting has been amended. The new protocol is indicated by amendment (a) and will be used to conduct the study in place of any preceding version.

The overall changes made to this protocol are as follows:

- Updated CDK4/6 to CDK4 and CDK6 throughout the document
- Updated the statistical analyses and statistical methods in Synopsis, Sections 8.1 Summary of Study Design, 12.1 Determinattion of Sample Size, 12.2.6 Primary Outcome and Methodology, 12.2.7.1 Overall Survival, and 12.2.14.2 Efficacy Interim Analyses
- Incorporated rationale for amendment Section 5.1 Rationale for Amendment (a)
- Incorporated Table JPBM 9.2 Toxicity D se Adjustments and Delays of Blinded Study Drug for Study JPBM for clarification
- Clarified dose suspension and dose reduction for Grade 3 hematologic toxicity and growth factor administration Section 9. .1.1.3 Hematologic Toxicity
- Clarified supportive management of diarrhea Sections 9.4.1.1.4.1 Diarrhea and 9.6.5 Supportive Management for Diarrhea
- Clarified emergency unblinding if patient discontinues treatment Section 9.5.2 Emergency Unblinding
- Incorporated information on substrate drugs of CYPs with narrow therapeutic margin in Section 9.6 Concomitant Therapy and Attachment 8 Protocol JPBL Inducers and Strong Inhibitors of CYP3A4 or Substrates of CYPs with Narrow Therapeutic Range
- Clarified growth factor administration Section 9.6.4 Growth Factors
- Clarified local ECG follow-up after C4D1 Attachment 1 Study Schedule

Minor typographical and formatting edits were made throughout the document for clarity and consistency.

Revised Protocol Sections

Note:	Deletions have been identified by ~~strikethroughs~~. Additions have been identified by the use of underscore.

2. Synopsis

Study Rationale

LY2835219 is an oral, selective, and potent small molecule cyclin-dependent kinase (CDK) 4 and 6 (CDK4~~/6~~ and CDK6) dual inhibitor with antitumor activity within multiple preclinical pharmacology models and an acceptable toxicity profile in nonclinical species. LY2835219 mesylate has been shown to significantly inhibit tumor growth in multiple murine xenograft models for human cancer. Studies with LY2835219 across breast cancer cell lines indicate differential sensitivity to CDK4~~/6~~ and CDK6 inhibition based on histological and genetic characteristics. Growth inhibition in vitro across a diverse panel of 46 breast cancer cell lines, representing the known molecular subgroups of breast cancer, indicates that sensitivity to CDK4~~/6~~ and CDK6 inhibition is greater in estrogen receptor-positive (ER+) breast cancers with luminal histology.

Length of Study: approximately 91 months

Planned interim ~~analysis: 218~~analyses: 189 (approximately 70% of the planned) progression-free survival (PFS) events and 230 (approximately 85% of the planned) PFS events

Diagnosis and Main Criteria for Inclusion and Exclusions:

Patients will be excluded from the study if they meet any of the following criteria: 12) have visceral crisis,, lymphangitic spread, or leptomeningeal carcinomatosis; 13) have inflammatory breast cancer; 14) have clinical evidence or a history of central nervous system (CNS) metastasis; 15) are currently receiving or have previously received endocrine therapy for locoregionally recurrent or metastatic breast cancer; 16) have received prior (neo)adjuvant endocrine therapy with a disease-free interval :S12 months from completion of treatment; 17) are currently receiving or have previously received chemotherapy for locoregionally recurrent or metastatic breast cancer; 18) have received prior treatment with everolimus; 19) have received prior treatment with any CDK4~~/6~~ and CDK6 inhibitor (or participated in any CDK4~~/6~~ and CDK6 inhibitor clinical trial for which treatment assignment is still blinded); 20) have initiated bisphosphonates or approved RANK ligand (RANK-L) targeted agents <7 days prior to randomization; 21) are currently receiving an investigational drug in a clinical trial or participating in any other type of medical research judged not to be scientifically or medically compatible with this study; 22) have received treatment with a drug that has not received regulatory approval for any indication within 14 or 21 days of randomization for a nonmyelosuppressive or myelosuppressive agent, respectively; 23) have had major surgery within 14 days prior to randomization; 24) have received recent (within 28 days prior to rrandomization) yellow fever vaccination; 25) have serious preexisting medical conditions that, in the judgment of the investigator, would preclude participation in this study; 26) have a personal history of any of the following conditions: syncope of cardiovascular etiology, ventricular tachycardia, ventricular fibrillation, or sudden cardiac arrest; 27) have a history of any other cancer (except non-melanoma skin cancer or carcinoma in-situ of the cervix), unless in complete remission with no therapy for a minimum of 3 years; 28) have received an autologous or allogeneic stem-cell transplant; 29) have active bacterial or fungal infection or detectable viral infection.

Statistical Methods:

Statistical:
A 3-look group sequential design on the primary endpoint of PFS will be utilized, with 2 interim ~~and primary PFS~~ analyses and 1 final PFS analysis occurring at approximately ~~218 PFS events~~189, 230, and ~~312~~270 investigator-assessed PFS events, respectively. ~~The Lan-DeMets method, utilizing a power~~A fixed alpha-spending ~~function with a power parameter of 14,~~method will be used to maintain the cumulative 1-sided type I error rate of .025. Assuming a hazard ratio of 0.~~714~~67, this design yields ~~at least~~more than 80% statistical power to detect superiority of the LY2835219 plus NSAI arm over placebo plus NSAI arm with the use of a 1-sided log-rank test and a cumulative type I error rate of 0.025.
OS is an important secondary endpoint for this study. OS will be tested only if the test of PFS is significant. The final OS analysis will ~~be tested~~occur after approximately 315 OS events have been observed~~, with a cumulative 1-sided type I error rate of .025. The test of OS will be a pooled analysis including a subset of patients from Study I3Y-MC-JPBL~~.

5. Introduction

Breast can er is one of the most common cancers in women. In 2012, there were approximately 1.7 million new cases of breast cancer worldwide; since 2008, the worldwide incidence of breast cancer has increased by more than 20% and mortality has increased by 14% (Bray et al. 2013; Ferlay et al. 2013). While early stage disease is treatable, patients with metastatic breast cancer (mBC) have a median overall survival (OS) of only 2 to 3 years (Cardoso et al. 2012). The treatment for women diagnosed with hormone receptor positive (HR~~+~~+) mBC includes

endocrine therapy. In postmenopausal women, aromatase inhibitors (including anastrozole and letrozole) are recommended for the initial treatment of mBC, if not used in the adjuvant setting or if discontinued for at least 12 months (Cardoso et al. 2012). However, de novo or acquired resistance to adjuvant endocrine therapy and metastatic breast cancer remains an important clinical challenge.

Cyclin D1 interacts with cyclin-dependent kinases 4 and 6 (hereafter CDK4~~/6~~ and CDK6) in an active protein complex that promotes cell proliferation (Velasco-Velazquez et al. 2011). Many HR+ breast cancers demonstrate an intact retinoblastoma tumor suppressive function, however, overexpression of cyclin D1 protein by oncogenic signaling occurs in approximately 30% to 50% of cancers. Cyclin D1 is regarded as the most frequently overexpressed gene in primary breast cancer, with amplification of the encoding gene, CCND1, occurring in approximately 15% of breast cancers (Casimiro et al. 2014). Therefore, CDK4~~/6~~ and CDK6 represents a potential therapeutic target for HR+ breast cancer. Consequently, further evaluation of CDK4~~/6~~ and CDK6 inhibitors to improve clinical outcomes for women with HR+ breast cancer is warranted.

During the cell cycle, the G1 restriction point controls entry into S phase and is essential for proper regulation of cell proliferation (Sherr 1996; Ortega et al. 2002). CDK4~~/6~~ and CDK6 participates in a complex with the D-type cyclins to initiate progression through the G1 restriction point. The CDK4~~/6~~ and CDK6 - cyclin D1 complex regulates the G1 restriction point through phosphorylation and inactivation of the retinoblastoma (Rb) tumor suppressor protein, thereby promoting S phase entry. Alterations in this pathway occur frequently in human cancers and involve: 1) loss of functional CDK inhibitors through deletion or epigenetic silencing; 2) activating mutations and/or overexpression of CDK4~~/6~~ and CDK6 or the D-type cyclins; and 3) loss of functional Rb through mutation or deletion. Except for tumors with functional loss of Rb, which functions downstream of the CDK4~~/6~~ and CDK6 - cyclin D1 complex, most cancers are potentially sensitive to pharmacologic inhibition of CDK4~~/6~~ and CDK6. From a therapeutic standpoint, the goal of inhibiting CDK4~~/6~~ and CDK6 with a small molecule is to prevent cell cycle progression through the G1 restriction point, thus arresting tumor growth.

LY2835219 represents a selective and potent small molecule inhibitor of CDK4~~/6~~ and CDK6 with acceptable physical characteristics, pharmacokinetic (PK) properties, and safety profile in nonclinical species. There may be important opportunities to tailor therapy with LY2835219 for pattiients with breast cancer. Specifically, studies with LY2835219 indicate differential sensitivity to CDK4~~/6~~ and CDK6 inhibition based on histological and genetic characteristics. Growth inhibition in vitro across a diverse panel of 46 breast cancer cell lines, representing tthe known molecular subgroups of breast cancer, indicates that sensitivity to CDK4~~/6~~ a d CDK6 inhibition is greater in ER+ breast cancers with luminal histology. In accordance with the known biology of CDK4~~/6~~ and CDK6, the results also indicate that many of these sensitive cell lines are also characterized as having amplification of CCND1, which is the gene that encodes cyclin D1. These results are consistent with previous studies which demonstrate that effective induction of G1 cell cycle arrest by LY2835219 is dependent upon the presence of Rb.

5.1. Rationale for Amendment (a)

Study JPBM protocol was amended to update the dosing guidance for cases of hematologic toxicity and diarrhea and guidance on the use of blood cell growth factors. Lilly conducted a review across several clinical trials ofabemaciclib in breast cancer and concluded that there were some inconsistencies. This amendment will harmonize the dosing guidance and clarify that blood cell growth factors are only to be used in a manner consistent with American Society of Clinical Oncology (ASCO) guidelines.

Further modifications were performed for clarity with supportive management for diarrhea and coadministration with substrate drugs of CYPs with narrow therapeutic margin.

Furthermore, the statistical analysis plan (SAP) was updated. The number of events required to perform the final PFS analysis was decreased from 312 events to 270 events based on the following rationale. The results of PALOMA-1 (palbociclib + letrozole vs letrozole) and PALOMA-3 (palbociclib + fulvestrant vs fulvestrant) indicate the effect of CDK 4 and 6 inhibitors in combination with endocrine therapy may have a larger effect than w s originally assumed during the development of this protocol. As a result, the assumed hazard ratio has been changed from 0.714 (corresponding to an increase in median PFS from 10 months to 14 months) to 0.67 (increase in median PFS from 10 months to 15 months). In addition, the interim analysis boundaries, timing of interim analyses, and OS analysis plan were modified.

Minor typographical and formatting edits were made throughou the document for clarity and consistency.

7.2. Exclusion Criteria

Patients will be excluded from the study if they meet **any** of the following criteria:

[19] have received prior treatment with any CDK4~~/6~~ and CDK6 inhibitor (or participated in any CDK4~~/6~~ and CDK6 inhibitor clinical trial for which treatment assignment is still blinded)

8.1. Summary of Study Design

Database lock for the inter m ~~analysis~~analyses for efficacy will occur when approximately ~~218~~189 and 230 investigator-assessed PFS events have been observed. Database lock for the ~~primary~~final analysi of the PFS endpoint will occur when approximately ~~312~~270 investigator-assessed PFS eve ts have been observed. The final analysis of OS will occur when approximately 315 OS events have been observed. All patients will be followed for survival information until death or study completion, whichever comes first.

9.4.1.1. Dose Adjustments and Delays

Table JPBM.9.2. Toxicity Dose Adjustments and Delays of Blinded Study Drug for Study JPBM

Toxicity Type	Toxicity Profile and Severity	Dose Suspension	Dose Reduction
Hematologic Toxicity Section 9.4.1.1.3	Grade 3	Dose **MUST** be suspended until toxicity resolves to at least Grade 2.	Dose **MAY** be reduced by 1 dose level - investigator's discretion.
Hematologic Toxicity Section 9.4.1.1.3	Recurrent Grade 3	Dose **MUST** be suspended until toxicity resolves to at least Grade 2.	Dose **MUST** be reduced by 1 dose level
Hematologic Toxicity Section 9.4.1.1.3	Grade 4	Dose **MUST** be suspended until toxicity resolves to at least Grade 2.	Dose **MUST** be reduced by 1 dose lev l.
Hematologic toxicity: **Patient requires administration of blood cell growth factors** Sections 9.4.1.1.3 and 9.6.4	Regardless of severity (Growth factors use according to ASCO Guidelines)	Dose **MUST** be suspended for at least 48 hours after the last dose of blood cell growth factors was administered and until toxicity resolves to at least Grade 2	Dos **MUST** be reduced by 1 dose level unless already performed for incidence of toxicity that lead to the use of growth factor.
Nonhematologic Toxicity (except diarrhea) Section 9.4.1.1.4	Persistent or recurrentt Grade 2 that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Dose **MAY** be suspended until t xicity resolves to either baseline or Grade 1.	Dose **MAY** be reduced by 1 dose level - investigator's discretion.
Nonhematologic Toxicity Section 9.4.1.1.4	Grade 3 or 4	Dose **MUST** be suspended until toxicity resolves to either baseline or Grade 1.	Dose **MUST** be reduced by 1 dose level.
Diarrhea Section 9.4.1.1.4.1	Requires hospitaliza ion or Grade 3 or 4	Dose **MUST** be suspended until toxicity resolves to at least Grade 1.	Dose **MUST** be reduced by 1 dose level.
Diarrhea Section 9.4.1.1.4.1	Persistent or recurrent Grade 2 that does not resolve with maximal s pportive measures within 24 hours to at least Grade 1	Dose **SHOULD** be suspended until toxicity resolves to at least Grade 1.	Dose **MAY** be reduced by 1 dose level - investigator's discretion.
Diarrhea Section 9.4.1.1.4.1	Diarrhea recurs despite maximal supportive measures after resuming same dose level after initial Grade 2 diarrhea	Dose **MUST** be suspended until toxicity resolves to at least Grade 1.	Dose **MUST** be reduced by 1 dose level.

Abbreviation: ASCO = American Society of Clinical Oncology.

Note: MAY = per the investigator's clinical judgment; SHOULD = not mandatory but highly recommended; MUST = mandatory.

Table JPBM.9.2~~.~~3. Dose Adjustments for Blinded Study Drug

9.4.1.1.3. Hematologic Toxicity

If a patient experiences Grade 4 hematologic toxicity, then dosing must be suspended (until the toxicity resolves to ~~either baseline or~~ at least Grade 2) and the dose of blinded study drug must be reduced by one dose level as outlined in ~~Table JPBM.9.2.~~ Table JPBM.9.3.

If a patient experiences Grade 3 hematologic toxicity, then dosing must be suspended (until the toxicity resolves to ~~either baseline or~~ at least Grade 2) and the dose of blinded study drug may be reduced by one dose level as outlined in ~~Table JPBM.9.2~~ Table JPBM.9.3 at the discretion of the investigator. If the patient experiences a recurrent episode of Grade 3 hematologic toxicity, the dosing must be suspended (until the toxicity resolves to at least Grade 2) and the dose of blinded study must be reduced by 1 dose level.

If a patient requires administration of blood cell growth factors, the dose of study drug must be suspended for at least 48 hours after the last dose of blood cell growth factors was administered and until toxicity resolves to at least Grade 2 then reduced by 1 dose level, if a dose reduction for the specific event necessitating the use of the growth factors has not already occurred.

Before the start of each cycle, hematologic toxicity must resolve to ~~either baseline or~~ at least Grade 2.

9.4.1.1.4.1. Diarrhea

A patient experiencing diarrhea requiiring hospitalization (irrespective of grade, that is, requiring intravenous [IV] rehydration) or severe diarrhea (Grade 3 or 4; see Attachment 9) must have study treatment suspended (until the toxicity resolves to ~~either baseline or~~ at least Grade 1) and must have the blinded study drug dose reduced by one dose level as outlined in ~~Table JPBM.9.2~~ Table JPBM.9.3.

If a patient experiences persistent or recurrent Grade 2 diarrhea that does not resolve with maximal supportive measures (refer to Section 9.6.5) within ~~3 days to either baseline or~~24 hours to at least Grade 1, then study trea ment should be suspended (until the toxicity resolves to ~~either baseline or~~ at least Grade 1) and the dose of blinded study drug may be reduced by one dose level as outlined in ~~Table JPBM.9.2~~Table JPBM.9.3 at the discretion of the investigator. If the same dose level was resumed and diarrhea recurs despite maximal supportive measures, the dose ofblinded study drug must be reduced by one dose level as outlined in ~~Table JPBM.9.2~~ Table JPBM.9.3

9.5.2. Emergency Unblinding

Emergency unblinding for AEs must be performed through the IWRS. This option may be used ONLY if the patient's acute well-being requires knowledge of the patient's treatment ass gnment~~.~~ or if a patient discontinues treatment due to disease progression based upon RECIST 1.1 (see Attachment 5) and knowledge of the patient's treatment assignment is deemed essential to the selection of the patient's next treatment regimen. In the case of disease progression, the investigator must consult with the Lilly CRP prior to unblinding.

9.6. Concomitant Therapy

Radiolabeled human disposition study indicates that LY2835219 is mostly cleared by oxidative metabolism and therefore inhibitors and or inducers of CYP3A may alter the metabolism of LY2835219. Based on these findings, grapefruit juice as well as inducers (for example, phenytoin or carbamazepine) and strong inhibitors of ~~CYP3A4~~CYP3A should be substituted or avoided if possible (Attachment 8). All patients may receive supportive therapy with dexamethasone, preferably :S7 days, if clinically indicated. Patients requiring more than 7 days of dexamethasone therapy will not incur a protocol deviation.

In addition, in vitro studies in ~~primary cultures of~~ cultured human hepatocytes indicate that ~~LY2835219 might inhibit the metabolism of~~ abemaciclib and its major metabolites LSN28395 7 and LSN3106726 down regulate mRNA of 1 or more CYPs, including CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2D6, and CYP3A, at clinically relevant concentrations. The mechanism of down regulation and its clinical relevance are presently not understood. Therefore, care should be taken when coadministering substrate drugs ~~in vivo in humans. Based on this finding, bupropion and efavirenz, which are sensitive CYP2B6 substra es, should be substituted or avoided if possible.~~of the above CYPs with narrow therapeut c margin (Attachment 8).

9.6.4. Growth ~~Factor~~Factors

Growth factors should not be administered to enable a patient to satisfy study inclusion criteria.

Growth factors may be administered in accordance with A CO guidelines (Smith et al. ~~2006; Rizzo et al. 2008).~~2015). Dosing of blinded study drug must be suspended if the administration of growth factors is required and must not be recom enced within 48 hours of the last dose of growth factors having been administered. Following the administration of growth factors, the dose of blinded study drug must be reduced by 1 dose level, if a dose reduction for the specific event necessitating the use of the growth factors has not already occurred.

9.6.5. Supportive Management for Diarrhea

At randomization, patients should receive instructions on the management of diarrhea. In the event of diarrhea, supportive measures should be initiated as early as possible. These include the following:

- At the first sign of loose stools, the patient should initiate anti-diarrheal therapy (e.g. loperamide) and notify the investigator for further instructions and appropriate follow-up.
- ~~Site personnel should assess response within 1 to 3 days.~~
- ~~If diarrhea does not resolve with anti-diarrheal therapy within 3 days to either baseline or Grade 1, then dosing should be adjusted as outlined in Section 9.4.1.1.1.1 and Table JPBM.9.2.~~
- Patients should also be encouraged to drink fluids (e.g., 8 to 10 glasses of clear liquids per day).
- Site personnel should assess response within 24 hours.

- If diarrhea does not resolve with anti-diarrheal therapy within 24 hours to at least Grade 1, blinded study drug should be suspended until diarrhea is resolved to at least Grade 1.
- When blinded study drug recommences, dosing should be adjusted as outlined in Section 9.4.1.1.4.1 and Table JPBM.9.3

In ~~potentially~~ severe cases of diarrhea, the measuring of neutrophil counts and body temperature and proactive management of diarrhea with antidiarrheal agents should be considered.

If diarrhea is severe (requiring IV rehydration) and/or associated with fever or severe ~~(Grade 3 or 4)~~ neutropenia, broad-spectrum antibiotics such as fluoroquinolones must be prescribed.

Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting should be carefully monitored and given intravenous fluid (IV hydration) and electrolyte replacement.

10.1.2. Efficacy Assessments during Postdiscontinuation Follow-Up

For those patients who are randomized and never receive study treatment or those who discontinue study treatment without objectively measured PD, the investigative sites will continue to monitor patients and periodically evaluate tumor response approximately every 8 weeks for the first 18 months following randomization and thereafter approximately every 12 weeks by the same method used at baseline and throughout the study until the patient has objective disease progression, or until the ~~primary~~final analysis of PFS. In addition, anticancer therapies initiated after study treatment discontinuation will be collected during this follow-up period. After the patient has objective disease progression, radiologic imaging and photographic images are no longer required and the patient will be followed up approximately every 12 weeks until the patient's death or overall study completion.

10.4.2.1. Archived Tumor Tissue

In tumor tissue samples, the CDK4~~/6~~ and CDK6 pathway components (for example, Rb) and markers relevant to breast cancer pathogenesis may be evaluated to assess any potential correlation with response to LY2835219. Tumor samples may be analyzed to explore potential tumor gene signature(s) associated with response or resistance to LY2835219 therapy. These studies may be analyzed at a laboratory designated by the sponsor and may include IHC of proteins, FISH for copy number amplifications, RNA gene-expression profiling, and/or genetic analyses of the tumor specimen DNA. Such analyses may employ targeted or high-throughput sequencing approaches. For this purpose, the results of this analysis will be correlated with clinical efficacy data.

12.1. Determination of Sample Size

A 3-look group-sequential design of the primary endpoint will be used to accommodate an event-driven plan for the interim and ~~primary~~final PFS analyses (see Section 12.2.6 for details). The ~~primary~~final PFS analysis will be performed after approximately ~~312~~ 270 PFS events have occurred (that is, a ~~30%~~ 40% censoring rate). Assuming a hazard ratio of 0.~~714~~67, this sample size yields ~~at least~~more than 80% statistical power to detect superiority of the LY2835219 plus

NSAI arm over the placebo plus NSAI arm with the use of a 1-sided log-rank test and a cumulative type I error of 0.025. If the true median PFS for the placebo plus NSAI arm is 10 months, then the hazard ratio of 0.~~714~~67 amounts to an approximately 4~~0~~5-month (~~40~~50%) improvement in median PFS for the LY2835219 plus NSAI arm under an additional assumption of exponential survival distribution. ~~Assuming approximately 10% screening failure, the study will enter approximately 500 patients.~~

12.2.6. Primary Outcome and Methodology

The 3-look group-sequential design of the primary endpoint will be used to accommodate an event-driven plan for the interim and ~~primary analysis.~~final analyses. There ~~is 1~~are 2 planned interim ~~analysis~~analyses and 1 ~~primary~~final analysis for PFS in this study. The interim ~~analysis is~~analyses are planned to take place after approximately ~~218~~189 (approximately 70% of the planned) investigator-assessed PFS events have occurred. ~~and~~ approximately 230 (appr ximately 85% of the planned) investigator-assessed PFS events have occurred. The cumulative 1-sided type I error rate of .025 will be maintained using the ~~Lan-DeMets method. Specifically, a power a-spending function with a power parameter (rho) of 14 will be used for this interim efficacy~~ following method. At the first and second interim analysis, the nominal alpha levels will be 0.0001 and 0.00015, respectively. The remaining alpha will be spent a the final analysis. The resulting boundary p-value for the final analysiss is dependent on the exact number of events observed at each analysis~~:~~

$$\text{—}^{*}(\ ) = \text{—}^{*}\ ^{14}_{k}\text{-}$$

~~Here, t_k is the information fraction at time k, and a is the cumulative 1-sided type 1 error rate, .025.~~

~~Therefore, if the interim analysis is~~ and can be calculated using the method of Slud and Wei (1982). If the 3 analyses are performed ~~after~~at exactly ~~218 events have been observed, a nominal 1-sided p-value of less than 0.00016 (corresponding approximately to an observed hazard ratio <0.6 under an exponential model) will need to be observed to declare statistical significance (see Table JPBM.12.2).~~

~~Table JPBM.12.2. Properties of Design for Progression-Free Survival~~

~~Information Fraction~~	~~Cumulative Events~~	~~Cumulative Alpha Spent~~	~~Cumulative Beta Spent~~	~~Boundary Reject H_0 (one-sided p-value)~~
~~0.7~~	~~218~~	~~0.000169~~	~~0~~	~~<0.000169~~
~~1.0~~	~~312~~	~~0.025~~	~~0.2~~	~~<0.024997~~

~~Abbreviation: H_0 = null hypothesis.~~

189, 230, and 270 events, then the boundary p-value at the final analysis will be 0.0249994. The actual ~~alpha spent~~ boundary for the final analysis will be calculated based on the actual number of events observed at the time of each analysis using software that implements the alpha-

spending ~~function~~ scheme noted above (for example, ADDPLAN 6.0 ~~or~~, SAS 9.2, or similar software).

~~If the~~ If statistical significance is not declared at the first interim PFS analysis, the second interim ~~analysis crosses~~ PFS analysis will be performed after 230 PFS events have been observed. Note that the ~~boundary~~ second interim analysis of PFS will only be performed if statistical significance is not declared at the ~~pre-specified level, this analysis will be considered the primary~~ first interim PFS analysis. If statistical significance is not ~~declared~~observed at ~~the~~ either interim ~~PFS~~ analysis, the ~~primary~~ final PFS analysis will be performed after approximately ~~312~~ 270 PFS events have been observed based on investigator assessment.

~~There is no intent to stop the study if the interim analysis crosses the boundary of significa ce at the pre-specified level. Treatment and follow-up of patients per the study schedule (Attachment 1) will continue and patients will not be crossed over. The study will continue and the pre-specified analysis of PFS at 312 events will be performed to meet requirements of certain regulatory authorities. The study will only be stopped early if both the DMC and global regulatory authorities agree that the scientific objectivess of the study are clearly met and unequivocal.~~

Once statistical significance is declared at either interim analysis o the final analysis, the study will be positive based on the primary endpoint of PFS, and testing of secondary endpoints will proceed as described in the SAP.

The interim PFS analyses will be performed by DMC. The requirements for unblinding the sponsor at the interim analyses are found in Section 12.2.14.

The primary test of PFS wiill compare the 2 treatment groups using a log-rank test stratified by the randomization factors.

12.2.7.1. Overalll Surviva

Overall survival is an important s condary endpoint for this study. ~~Given that a hazard ratio for the effect of LY2835219 on O is anticipated to be smaller than that anticipated for PFS, to improve the precision of estimating the effect of LY2835219 on OS in this setting, a pooled analysis is planned for t e main analysis of OS. As noted in the Food and Drug Administration (FDA) Guidance for Industry on Integrated Summary of Effectiveness (2008) and in the EMA Guidance "Points to Consider on Application with 1.Meta-analyses; 2.One Pivotal Study (CPMP/EWP/2330/99, 2001)," an appropriate use of pooled analyses is during the assessment of drug effects on a secondary endpoint that requires more power than the individual trials can provide.~~

~~Study I3Y-MC-JPBL (JPBL) is a study which randomizes patients with either locally advanced disease not amenable to curative treatment by surgery or metastatic disease to LY2835219 plus fulvestrant or placebo plus fulvestrant as either a first or second therapy for locally advanced or metastatic disease.~~

~~Given the inclusion of patients receiving a first therapy for locally advanced or metastatic disease in the 2 trials (Studies JPBL and JPBM), that patients in both studies receive endocrine therapy in combination with LY2835219 or placebo, and the similarity of the study schedules (Attachment 1), it is rational and scientifically valid to conduct a pooled OS analysis using all patients from Study JPBM and those patients from Study JPBL who receive initial therapy for locally advanced or metastatic disease on study.~~

To maintain the study-wise type I error rate, OS will be hierarchically tested~~. Overall survival~~; that is, OS will only be tested inferentially for significance only if the test of PFS is significant~~, and an alpha-spending scheme will be employed to maintain a study-wise type I error rate of .025. The final pooled OS analysis will occur when at least 315 OS events have been obsserved events in Study JPBM and all events for the final analysis have been observed in Study JPBL, as specified in the study's protocol. Note: while the pooled analysis is considered the pri ary OS analysis for this study, a subgroup analysis of Study JPBM OS data alone will be performed for descriptive purposes~~. Further details ~~of the pooled testing of OS, including interim analyses, are described in the Study JPBM~~ will be in the study SAP.

12.2.14.2. Efficacy 1nterim Analyses

~~One~~Two efficacy interim ~~analysis~~analyses of PFS ~~and 1 interim analysis of pooled OS data~~ are planned, as described in ~~Sections~~ Section 12.2.6 ~~and 12.2.7.~~

. Four interim analyses of OS are planned (at the time of each of the 2 interim PFS analyses, at the time of the final PFS analysis, and at the time when approximately 75% of the OS events have been observed; subsequently, a final OS analysis is planned).

The interim PFS ~~analysis~~analyses will be conducted to provide early efficacy information and could potentially result in early communication with regulatory agencies. This analysis will be performed by an independent Statistical Analysis Group and provided to the DMC. ~~.~~The DMC should recommend unblinding the spo sor if the following are observed:

- The analysis of investigator-assessed PFS is significant at the alpha level specified in Section 12.2.6 with the observed stratified hazard ratio for investigator-assessed PFS less than 0.56 at the first interim analysis, or is less than 0.6 at the second interim analysis, and
- Results of the analysis of the centrallyreviewed PFS support the results of the investigator-assessed PFS analysis.

If the analysis of PFS is positive based on these requirements, the DMC will be instructed to recomme d to the SMD that the sponsor be unblinded. The SMD may convene an IRC to review the DMC's recommendation prior to sponsor unblinding.

O erall survival will be analyzed as described in Section 12.2.7. Results of OS analyses will not be communicated until a significant result is observed or the final PFS analysis is performed.

The sponsor has no intent to stop the study based on interim analysis of efficacy, and all patients will continue follow-up for PFS until the primary PFS analysis and for OS until study close. Patients randomized to the control group will not be permitted to cross over to the experimental group, as this will confound the assessment of OS. In addition, patients will remain blinded forr the duration of the study unless the criteria in Section 9.5 are met. If the DMC makes a recommendation counter to this, for example, the DMC recommends crossing all patients over to the experimental treatment, FDA will be consulted before any action is taken as well as other regulatory agencies if deemed appropriate.

14. References

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Attachment 1. Protocol JPBM Study Schedule

Protocol I3Y-MC-JPBM During Treatment Study Schedule			Study Treatment Period						
		Cycle / Visit	1	2		3	4-X		
		Approximate Visit Duration (days)	28	28		28	28		
		Relative day within a cycle	1	1	21-28	1	1	21-28	
Procedure Category	**Procedure**	**Protocol Reference**							**Comments**
Physical Examination	Physical Exam		X	X		X	X		Include but not limited to weight
	Vital Signs		X	X		X	X		Include blood pressure, pulse, respiratory rate, and temperature
	ECOG performance status	**Attachment 4**	X	X		X	X		
Archived Tumor Tissue		**Section 10.4.2.1**	X						Whole or partial block or 15 - 20 slides should be provided upon patient randomization.
Adverse Event Collection/CTCAE Grading		**Section 10.3**	X	X		X	X		
Concomitant Medication Notation		**Section 9.6**	X	X		X	X		

Protocol I3Y-MC-JPBM

During Treatment Study Schedule

Procedure Category	Procedure	Protocol Reference	Study Treatment Period						Comments
		Cycle / Visit	**1**	**2**		**3**	**4-X**		
		Approximate Visit Duration (days)	28	28		28	28		
		Relative day within a cycle	1	1	21-28	1	1	21-28	
Lab/ Diagnostic Tests	Central hematology	**Attachment 2**	X	X		X	X		Central h matology labs may be drawn up to 3 days prior to Day 1 of each cycle. Additional local hematology labs may be drawn for treatment adjustment and patient management purposes.
	Central chemistry	**Attachment 2**	X	X		X	X		Central chemistry labs may be drawn up to 3 days prior to Day 1 of each cycle. Additional local chemistry labs may be drawn for treatment adjustment and patient management purposes.
	Pharmacokinetic (PK) sampling	**Attachment 7**	X	X		X			See Attachment 7 for specific timing.
	Pharmacogenetic blood sample	**Section 10.4.2.2**	X						Draw sample before patient is dosed on C1D1.
	Biomarker plasma sample	**Section 10.4.2**	X	X					Draw sample before patient is dosed on C1D1 and upon arrival at site on C2D1.
	Local ECG	**Section 10.3.2.1**	X	X			X		2 to 4 hours after the LY dose on Cycle 1 Day 1, upon arrival at site on Cycle 2 Day 1, 2 to 4 hours after the LY dose on Cycle 4 Day 1. Following C4D1, no additional ECGs are required while the patient is on treatment (only subsequently for short-term follow-up). Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

Abbreviations: C4D1 = Cycle 4 Day 1; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-BR23 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Breast cancer; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D 5L = EuroQol 5-Dimension 5 Level; MRI = magnetic resonance imaging; RECIST = Response Evaluation Criteria in Solid Tumors.

Protocol I3Y-MC-JPBM

Study Schedule for the Continued Access Period only

		Study Period	Patients on Study Treatment	Continued Access Period Follow-Up	
		Cycle	X	Follow-Up[a]	
		Visit	501-5XX	901	
		Approximate Visit Duration (days)	28±3	30±5	
		Relative day within a cycle	1		
Procedure Category	**Procedure**	**Protocol Reference**			**Comments**
Adverse Events Collection/CTCAE Grading		**Section 10.3**	X	X	Data on SAEs that occur before the end of trial will be stored in the collection database and the Lilly safety system
Study Drug	LY2835219	**Section 9.1**	X		Only patients assigned to LY2835219 at randomization and receiving clinical benefit will continue to receive LY2835219 during the continued access period. LY2835219 is to be administered orally every 12 hours on Days 1 through 28 of each cycle. Patients who were assigned to placebo, will no longer receive placebo during the continued access period and cannot crossover to LY2835219.
Co-Administered Drugs	Anastrozole	**Section 9.1**	X		Patients receiving clinical benefit will continue to receive anastrozole or letrozole during the continued access period. Anastrozole or letrozole is to be administered orally every 24 hours on Days 1 through 28 of each cycle
	Letrozole	**Section 9.1**	X		

Attachment 8. Protocol JPBM 1nducers ~~and~~, Strong 1nhibitors of ~~CYP3A4~~CYP3A, or Substrates of CYPs with Narrow Therapeutic Range

Inducers of ~~CYP3A4~~ CYP3A
Carbamazepine
Dexamethasone[a]
Phenobarbital/phenobarbitone
Phenytoin
Rifapentine
Rifampin
Rifabutin
St. John's wort

[a] Important note: All patients may receive supportive therapy with dexamethasone, preferably ≤7 days, if clinically indicated.

Strong inhibitors of ~~CYP3A4~~ CYP3A
All HIV protease inhibitors
Clarithromycin
Itraconazole
Ketoconazole
Nefazodone

~~a Important note: All patients may receive supportive therapy with dexamethasone, preferably :S7 days, if clinically indicated. Patients requiring more than 7 days of dexamethaso e therapy will not incur a protocol deviation.~~

Cytochrome P450 Substrates with Narrow Therapeutic Range

Cytochrome P450	**Substrate**
CYP1A2	Theop ylline Tiz nidine
CYP2C8	Paclitaxel
CYP2C9	Warfarin Phenytoin
CYP2D6	Thioridazine Pimozide
CYP3A	Alfentanil Astemizole Cisapride Cyclosporine Dihydroergotamine Ergotamine Fentanyl Pimozide Quinidine Sirolimus Tacrolimus Terfenidine

Attachment 9. Protocol JPBM CTCAE 4.03 Diarrhea Definition

Diarrhea will be evaluated in this study using the criteria proposed by Common Terminology Criteria for Adverse Events (CTCAE) v4.0 revised: CTCAE 4.03-June 14, 2010: Gastrointestinal disorders.

Gastrointestinal Disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline.	Increase of 4-6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase ≤=> 7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: a disorder characterized by frequent and watery bowel movements					

Abbreviation: ADL = Activities of Daily Living.

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